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ARCHIVES OF DISEASE IN CHILDHOOD

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The Journal of the British Paediatric Association

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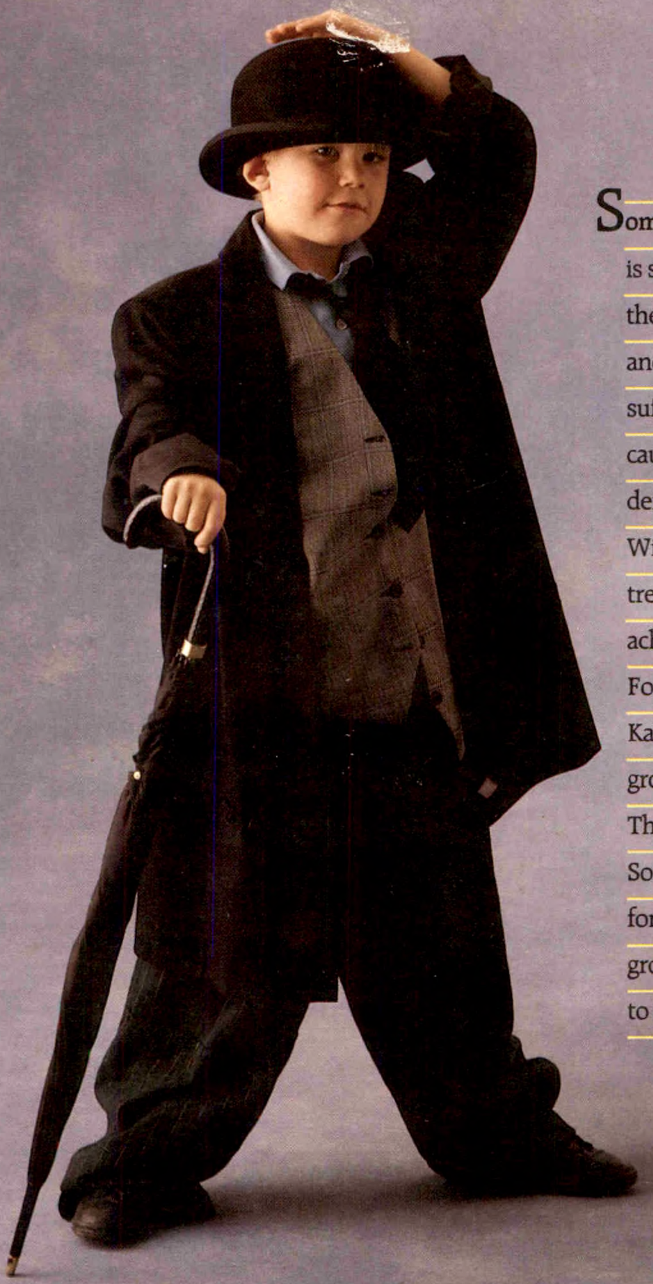

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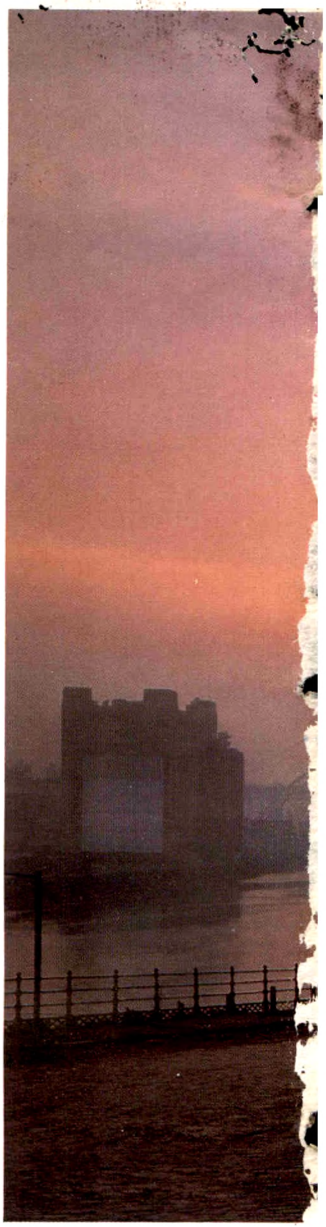

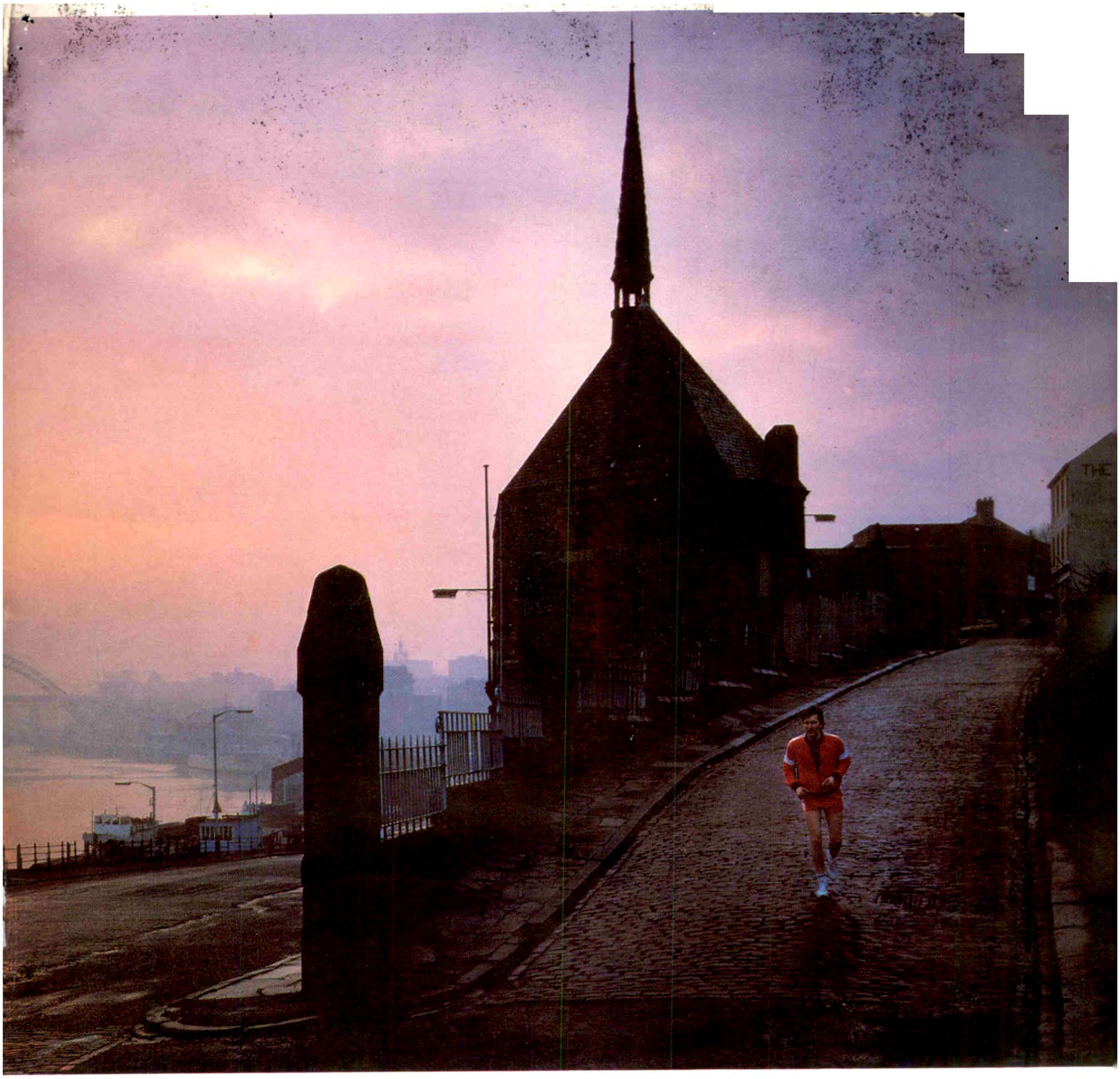

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Archives of Disease in Childhood, 1987, **62,** 1–2

Annotations

Hypermobility of joints

Individuals who have very loose joints have attracted medical curiosity since the time of Hippocrates, and those 'India rubber people' who also have stretchy skin now earn the appellation of the Ehlers-Danlos syndrome. It is only in the last three decades that more subtle patterns of hypermobility have been associated with common disorders of paediatric importance. Carter and Wilkinson devised clinical procedures to show that children who have congenital hip dysplasia and their first degree relatives tend towards generalised hypermobility.[1] Subsequent studies have shown other musculoskeletal associations of articular hypermobility and have drawn attention to the relatively common benign hypermobility syndrome.[2]

Diarthrodial joints are constrained from excessive motion by their surrounding soft tissues, primarily the joint capsule, as well as ligaments, tendons, adjacent muscles that move the joints, overlying subcutaneous tissues, and skin. At the biochemical level, the most important constituent of these tissues is type I collagen, a rope like macromolecule that is the most ubiquitous of body structural proteins. Collagen stiffens with aging as a result of increased diameter of assembled bundles of fibrils, as well as increase in the number of intermolecular crosslinks. Stiffness of collagen in ligaments, as assessed indirectly by measurement of joint mobility, increases throughout childhood and early adult life.[3 4] Clinical consequences of hypermobility are seen when the tensile resistance of articular constraining tissues differs from the normal for that age and also when inappropriate mechanical strain is imposed on those tissues by muscular activity. For example, intrauterine hypermobility predisposes to congenital hip dysplasia[1 5] and adolescent overindulgence in athleticism may precipitate the hypermobility syndrome.[2 6]

Assessment of hypermobility

Routine clinical assessment of hypermobility does not require special equipment. Mechanical devices reported for research purposes[3 7 8] have not supplanted the simple Carter-Wilkinson type of clinical manoeuvres.[1] In modified form,[4] the procedures are (1) passive apposition of the thumbs to the flexor aspect of the forearm, (2) passive dorsiflexion of the fifth fingers beyond 90°, (3) hyperextension of the elbows beyond 10°, (4) hyperextension of the knees beyond 10°, and (5) ability to place the palms of both hands flat on the floor with the knees held in extension. By this method a score can be assigned, with a maximum of nine, one point for each of the paired limb procedures and one point for spinal hypermobility; a mobility score of four or greater may be considered hypermobile. The spinal flexion test is the least useful in that performance is influenced by age, limb length, and even the repetitive hamstring stretching of ballet training.[9] Of course, hypermobility may be demonstrable in other joints such as the wrists or finger joints, and the latter may be particularly impressive in 'collagenopathies' such as Ehlers-Danlos syndrome. The frequency of abnormal mobility varies according to joint, with the knees and elbows remaining hypermobile later in life than the wrists or ankles The expectation that symptoms occur only in children who are *generally* hypermobile may lead to underrecognition of localised hypermobility associated symptoms.[6]

Hypermobility of joints is a common clinical finding and is not symptomatic in the majority of children. In general, girls have greater mobility of joints than boys of the same age, ranges are usually greater in the non-dominant limb, and Asians are more mobile than whites Carter and Wilkinson reported hypermobility in 7% of 285 healthy children aged 6 to 11 years.[1] A more recent American study found generalised hypermobility in 12% of normal schoolchildren and 66% of 32 children with 'juvenile episodic arthralgia'.[10]

Hypermobility syndrome

Kirk, Ansell, and Bywaters drew attention to a syndrome of recurring arthralgia, joint swelling, and muscle cramps in hypermobile persons, 75% of their patients being aged 16 years or younger [2] Patients with features of Ehlers-Danlos syndrome or Marfan's syndrome were excluded. This type of benign hypermobility probably represents the upper end of the normal range of joint mobility The hypermobility syndrome is a more common cause of musculoskeletal symptoms in teenagers, especially girls, than any of the varieties of inflammatory juvenile arthritis. The typical patient has recurrent pain and sometimes intermittent swelling in one or other knee. Polyarticular symptomatology is unusual and the differential diagnosis is most often between hypermobility and inflammatory joint disease. Although joint effusion occurs, presumably from mild traumatic synovitis, signs of active inflammation will be absent. Other common complaints include bruising and muscle cramps after physical activity. Often there is a history of a growth spurt preceding the onset of symptoms, and diagnostic clues in the family history may include congenital hip dislocation, scoliosis, and past occurrence of similar symptoms or 'growing pains' in a parent.

Associated disorders

As articular hypermobility is so common it may coexist with inflammatory joint disease. For this reason the hypermobility syndrome is a diagnosis of exclusion and simple laboratory tests for inflammatory rheumatic disease may be necessary to reassure both the doctor and the family.

Hypermobility accompanies a multitude of monogenic syndromes, such as osteogenesis imperfecta and other heritable disorders of connective tissue, and multifactorial syndromes, such as congenital hip dysplasia.[7] Most of these are readily recognisable by their concomitant features, and hypermobility will usually be an incidental or contributory physical finding rather than the primary mode of presentation. Occasionally, a hypermobile tall adolescent with recurring pain or swelling of a knee will also have the long limbs, arachnodactyly, and anterior chest deformity of Marfan's syndrome; this warrants special attention because of the late life threatening risk of aortic dilatation.

Management

Bracing of very lax and unstable joints may be necessary in patients who have gross hypermobility, usually associated with one of the collagenopathies such as Ehlers-Danlos syndrome type I. The same approach may help to preserve function when instability is due to the hypotonia of muscular or neuromuscular disease rather than ligamentous laxity.

In the benign hypermobility syndrome explanation of the basis of symptoms has particular therapeutic value. Recognition and demonstration of articular hypermobility in a child with previously mysterious aches and pains is often a source of satisfaction to both the patient and doctor, especially when there has been delay in diagnosis.[6] There may be anxiety that the child has potentially disabling arthritis, and this worry may have been fuelled by overinvestigation or overuse of drugs.[6] The fundamental problem is not inflammation, and most of these patients do not need anti-inflammatory medication. Symptoms generally resolve late in adolescence when periarticular tissues develop mature tensile resistance The strength of joint ligaments cannot be augmented by drugs, and the best that can be done is to strengthen the surrounding musculature. Usually this will mean having a physiotherapist instruct the child in quadriceps exercises, and regular swimming in the neighbourhood pool is a good form of physical treatment. Physical activity should not be restricted unless the child is clearly overindulging in gymnastics, competitive sports, or ballet. The children should be reassessed during adolescence because of the increased risk of scoliosis.

Later in life there is an increased liability to minor injuries,[9] hernias, varicose veins, pes planus, uterine prolapse, and other consequences of tissue laxity.[7] Fifty or 60 years later some who were hypermobile in childhood may be more susceptible to certain patterns of osteoarthritis,[2] but the evidence is no more than preliminary[11] and this should not alter the optimism of prognosis.

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Archives of Disease in Childhood, 1987, **62,** 3–5

The physically handicapped school leaver

"At root, it seems to me that the question of why we should be concerned with the plight of the handicapped is attitudinal. We should care because the handicapped are part of our humanity Despite our good intentions and the passage of legislation, our efforts to help do not seem to work out as intended in increasingly sophisticated, complicated and technological societies when the child (whose emotional appeal for fund-raising is very great) emerges into the adult world. The rejection of the handicapped adult may be because 'in some way they reveal to us who we are. We don't want to look at their weaknesses' . . . "[1]

Paediatricians will be familiar with the expressed sentiments on fundraising. They will, sadly, also have become used to the fact that many of those they have cared for, throughout childhood, and through a good proportion of the paediatrician's working life, have no job, no hopes, and a marginal existence; only a few of the less severely disabled will have developed a satisfactory adult lifestyle.

The extent of their needs has been documented many times yet the report and its recommendations detailing this seems not to be widely available [2]

As long ago as 1981 the Warnock report commented that the transition to adulthood was particularly difficult for the handicapped teenager: "The transition from school to adult life can be difficult for many young people. For those with special needs it is likely to be a period of particular stress".[3]

At the same time Castree and Walker looked at a group of young adults with spina bifida and compared them with a similar group of cerebral palsied adolescents in Newcastle.[4] They found that both groups had achieved a remarkable degree of independence in self care but the more severely handicapped of them had no work. Parents commented particularly on the poor contact with social services after leaving school and the difficulty they had in finding and mobilising help in a whole variety of areas. They also felt that the educational potential of their children was not realised.

This survey is referred to in a new supplement of the *Developmental Medicine and Child Neurology* series, 'The health and social needs of physically handicapped young adults: are they being met by the statutory services?'[1] The booklet makes easy, graphic, and sorry reading, which is worth summarising

Contact with the health services

"We have been told that it is hard for young adults to find speech therapists or other specialists to help them with feeding problems". Hirst showed that 70–92% had lost touch with therapists, dentists, and doctors who had seen them at school.[5]

Poor mobility

Many young people lose their hard won ability to walk and develop contractures when they leave school and no longer have regular physiotherapy. It is difficult to know whether they are then helped by orthopaedic referral.

Housing adaptations, provision, and repair of aids and equipment

Several reports document what many will know from experience: that there is often a considerable delay before a family is well housed and before adaptations are made. These areas are usually outside the remit of doctors, but the provision of aids or appliances and the development of a joint aids store may not be. Robson, reviewing the work of the Newcastle young adult clinic held in their aids centre, found many unsatisfactory or worn out appliances and was able to offer much help with this and with wheelchairs. (Robson BJ. Report on the Newcastle young adult clinic (YAC) for the disabled 1982. Unpublished report.)

Incontinence

Again there is little documented evidence relating specifically to young adults, although physically handicapped children have been shown to be in need of an adequate continence service[6] in which the investigation of incontinence is undertaken and is related to other disabilities.

Dental health

Little is known about the dental health of physically handicapped adults. Some districts do establish clinics, but these often rely heavily on one interested specialist or are not continued when he moves or retires.

Sexual and genetic counselling

Physically handicapped young people are less mobile than their peers; their knowledge of these matters is often rudimentary or faulty, they have little chance to 'pick up' information—whatever its quality, counselling is often poor or non-existent, and often the young people worry about the inheritance of their disability.

Maladjustment and psychiatric problems

These also occur at an increased rate sufficient to indicate that there is a need for access to psychiatric counselling for the young person and the family.

Education

Many children have lost much time and educational opportunity. One of the earlier documentations of this was that of Tuckey *et al,* 'Handicapped school-leavers, their further education, training, and employment'.[7] Further education has become more widely available since then as employment has contracted. Nevertheless, facilities are highly variable and the would be student will be limited by geography more than anything else. Recent findings are detailed in 'Beyond the school gate'.[8] Many authorities still do not recognise that they have a duty to provide for *all* young people who want continued further education between the ages of 16–19. It is worth recording that much helpful advice is available within the covers of 'After 16—what next?' published by the National Bureau for Handicapped Students.[9] The related publication 'After 16: the education of young people with special needs' urges action.[10]

Income

The Spastics Society report says unequivocably, 'Two main factors contribute to the financial hardship of families caring for a handicapped dependant—increased family expenditure and reduced family income. Hyman[11] has estimated that disability in one member of the household could cost as much as 20–25% of the household income.' It is noteworthy that the Fowler proposals intend that where a household has more than one handicapped member benefits shall only be paid to one. Many believe that disabled households face great hardship in the future.

Employment

The disabled are less likely to be in employment and even less likely to be in well paid, skilled work than their able bodied peers.

If open employment is difficult, sheltered employment, offering the benefits of a productive day with supervision, is a virtually non-existent option

Social life

Like disabled people of all ages, young adults usually find their contacts reduced In addition, these young people may never have acquired the social skills of those disabled later in life.

Why the problem?

In a word, then, the current situation is a shambles. At a time when the child is experiencing the oscillations and uncertainties of trying to emerge as an adult he is subject to constant threats to his supposedly independent status in that role. Those who have supported him through childhood have no statutory obligation to do so, indeed statutory demands on their time are heavy; parents are aging and finding much cause for anxiety. Health and social services fail him.

The Spastics Society contends this is for three reasons:

(a) Poorly organised services and few trained personnel.

(b) Poor coordination and communication between health and social services with little knowledge of the needs of the handicapped—the data base is usually absent.

(c) A poverty of information available to the handicapped person.

Possible solutions

One cannot quarrel with these findings: the evidence is too strong. Does one agree with the recipe for change, assuming that no concerned person would defend the status quo?

A district handicapped adult team is proposed, available to offer advice on all the matters detailed above, together with a young disabled adult clinic, in service training for involved professionals, and a registry. It is further proposed that local surveys of the numbers and needs of disabled populations should be undertaken. Finally, the team should include a physician with expertise in the management of handicap, a 'broader-based specialist in adolescent-adult handicap'—that is, a separate specialist from the consultant in neurological rehabilitation or medicinal disability.

How realistic is this? An 'at risk' register would be a useful data base, although how we should use it is not clear. The Southampton group have shown a great deal of stress in such families and suggested that rapid intervention (more support services at home with intermittent relief) would help if it were provided at crisis times.[12] Who would man such a computer register? What would be the chains of communication or command that would allow a flexible response from the several statutory bodies to be called up?

The young adult clinic has been shown to work. It is not advocated in so many words in an important new report 'Physical disability in 1986 and beyond' in which a section is devoted to the young adult.[13] But it is acknowledged that there should be an assessment centre and referral to an appropriate consultant should be made. This is the nub of the matter, perhaps.

As far as I know, the excellent umbrella of paediatric services found in most parts of the land did not arise spontaneously nor yet from isolated ventures by a variety of professionals. It arose from the work of concerned paediatricians who regarded it as their brief to establish what were considered necessary features at various times.

The Royal College of Physicians is rightly exercised by the fact that such services for disabled adults are lacking. They are a 'deprived population' able to call on few specific facilities and a paucity of consultants with specific expertise in the management of their disability problems (there are perhaps 50 of us in the United Kingdom). The plight of teenagers is but one face of this problem.

The college acknowledges that the UK is engaged on an important but unplanned experiment 'to set up an effective care service for the physically disabled without a substantial specialty of rehabilitation'. It goes on to recommend the equivalent of 10 sessions devoted to this per district, split between two to three consultants, and at regional unit level two full time consultant posts The report acknowledges that the health service needs to provide information, registers, key workers, committees, handicap teams as well as continence advisers, wheelchair clinics, and disabled living centres. Is it reasonable to expect these to arise separately and yet cohesively without the appointment of a consultant majoring in this commitment? It seems quite unrealistic for the Spastics Society to look for a subspecialist for adolescents when the corresponding adult specialist is still missing.

There may be the opportunity to create a few more consultant posts shortly. Perhaps paediatricians would feel able to persuade their adult (!) colleagues that one such appointment to a district and certainly to a teaching hospital could be catalytic in profoundly changing the current dismal situation of their teenage patients

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Inherited disorders of straight chain fatty acid oxidation

The first inherited disorder of organic acid metabolism was described in 1966, but it is only with the improvement in laboratory facilities in recent years that the true incidence of these disorders is beginning to be appreciated. Defects in the mitochondrial oxidation of straight chain fatty acids seem to be particularly common (as inborn errors of metabolism go) even though the first example, medium chain acyl-CoA dehydrogenase deficiency, was not properly characterised until 1982. That such a major group of disorders should appear on the scene so late testifies to difficulties in recognition and investigation that still remain major problems.

Biochemical background

The presently known inherited disorders of mitochondrial oxidation of straight chain fatty acids all affect the acyl-CoA dehydrogenase step Three different mitochondrial enzymes (abbreviated to LCAD, MCAD, and SCAD, respectively) catalyse the dehydrogenation of long chain, medium chain, and short chain acyl-CoAs. Deficiencies of each of these enzymes individually have now been recognised, though SCAD deficiency is rare, clinically distinct from the other types, and excluded from the following discussion In addition, disorders of the mitochondrial electron transfer chain give rise to a state of multiple dehydrogenation deficiency. A mild form, often known as ethylmalonic-adipic aciduria (EMA), can resemble MCAD deficiency clinically and in the pattern of urinary metabolites.

Some patients seem to have disorders of fatty acid oxidation that do not correspond to any of those so far defined, and we may expect deficiencies of other enzymes in the mitochondrial β oxidation pathway to be characterised within the next few years.

Clinical presentations

In all these disorders the inability to oxidise fats efficiently produces a tendency to fasting hypoglycaemia with inappropriately low ketonaemia accompanied, in severe attacks, by various secondary metabolic disturbances. The age of presentation is variable. LCAD deficiency is generally the earliest with three of the four patients so far fully described presenting soon after birth with hypoglycaemia, recurrent vomiting, liver dysfunction, cardiomegaly, and a tendency to cardiac arrest.[1] MCAD deficiency is more common and generally less severe. It usually presents after 6 months of age, maybe even in the teens, often with a Reye like syndrome after a viral illness. Some children with MCAD deficiency may have repeated attacks of hypoglycaemia under minimal stress but others are completely asymptomatic in the absence of severe precipitating factors, even though a sib has died of the disease. EMA, too, may present with an acute Reye like attack, but our limited experience suggests that this disorder tends also to produce chronic problems with failure to thrive.[2]

Diagnosis

The first step is to collect urine samples during an acute attack. Timing is vital as the urine may appear completely normal between crises. The samples should be sent to an experienced laboratory for examination of urinary acids by gas chromatography, preferably combined with mass spectrometry. The free monocarboxylic acids are not excreted in any quantity but a rich variety of secondary products,[3] particularly the even chain dicarboxylic acids, should be present during crisis in all these conditions. A rather similar dicarboxylic aciduria results from the administration of feeds containing medium chain triglycerides—for example, Pregestimil, Nenatal[4]—and it is always helpful (as well as being a matter of courtesy) to supply the investigating laboratory with brief clinical details and a full account of medication and feeds immediately before the collection of the specimen.

Sometimes the possibility of an acyl-CoA dehydrogenase deficiency may only be considered retrospectively after the attack or studies on asymptomatic sibs may be required, particularly in MCAD deficiency. In these cases it is usually possible to produce a diagnostic organic acid profile by fasting the patient, but this procedure has proved fatal and should only be undertaken with extreme caution. It may be necessary to prolong the fast well beyond 24 hours to be certain of a negative result. Fat loading is also intrinsically dangerous and should never be used. A safer approach using carnitine loading has recently been suggested[5] but requires extremely specialised laboratory facilities These problems may be circumvented by assaying the enzymes themselves, in cultured fibroblasts or in leucocytes. Methods suitable for large scale clinical application have recently been developed.[6] They will find increasing application as they become available routinely as it is often difficult to distinguish with certainty between the different types of defect on the basis of urinary organic acid profiles alone.

Treatment

During an acute attack the immediate aim is to restore the blood glucose concentration. On thus relieving the pressure to metabolise fatty acids many of the secondary biochemical problems will resolve automatically but, in severe cases with Reye like features, measures to deal with cerebral oedema and electrolyte imbalance may be necessary.

In deciding long term management it can be helpful to assess the patient's susceptibility to hypoglycaemia during the overnight fast. If this is pronounced, as it is likely to be in LCAD deficiency, frequent carbohydrate rich meals are indicated. Excessive fat intake should be avoided in all these conditions. Valproic acid should not be given as it is likely to be unusually toxic to these patients.

Refractory cases may need additional measures. Some patients with EMA improve markedly on large doses of riboflavin. In LCAD deficiency correction of secondary carnitine deficiency may be helpful, though this treatment may be harmful in EMA. Medium chain triglycerides may be substituted for normal dietary fat in LCAD deficiency, but this could be fatal in MCAD deficiency The diagnosis must be absolutely secure before these supplementary treatments are tried and it could be wise to consult an expert for the most up to date views in this rapidly developing field.

Many patients with MCAD deficiency are completely asymptomatic for long periods, indeed some may never show any sign of the abnormality, and it is important not to overreact to the diagnosis in a child who has had an isolated attack of hypoglycaemia. Appropriate advice on the dangers of prolonged fasting together with family studies to recognise other affected siblings are all that may be required

MCAD and LCAD deficiencies can be diagnosed prenatally using cultured amniotic fluid cells should this be necessary

The size of the problem

In the short time since the discovery of these conditions the number of cases known has increased rapidly. They seem to account for a small proportion of sudden infant deaths[7] and a somewhat larger proportion of cases of Reye's syndrome. MCAD deficiency, in its milder presentations, is probably often overlooked. Isolated attacks of hypoglycaemia at home are likely to be labelled 'fits' without their metabolic basis being appreciated, and febrile convulsions too may be indicative of MCAD deficiency. Full investigation of all patients with the less specific indications is quite beyond the capacity of current laboratory facilities Some form of preliminary screening, particularly a consistent and determined approach to the detection of intermittent hypoglycaemia, would produce a more manageable group for detailed investigation and should identify at least those patients most at risk of a severe attack.

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Original articles

The need to screen all retinoblastoma patients for esterase D activity: detection of submicroscopic chromosome deletions

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SUMMARY Roughly 5% of all patients with retinoblastoma carry a constitutional chromosome deletion on the long arm of chromosome 13, which confers a prezygotic predisposition to tumour development. As offspring of deletion carriers have a 50% risk of inheriting the predisposition locus it is important to identify deletion carriers. The site of the esterase D gene to the often deleted region offers an objective means of deletion identification. The chromosomes of a patient with unilateral retinoblastoma, previously supposed to have a normal karyotype, were re-examined after the discovery that his red blood cells contained reduced activities of esterase D. A small sub-band deletion was found in chromosome region 13q14. These findings emphasise the importance of measurements of esterase D in all patients with retinoblastoma, even those with an apparently normal karyotype.

Retinoblastoma is an intraocular tumour of children that affects roughly 1 in 20 000 live births.[1] There are both sporadic and hereditary forms. In the United Kingdom about 20–24% of cases are familial.[2] In about 5% of patients a prezygotic predisposition to tumour formation is associated with a somatic deletion, of variable length, from the long arm of one copy of chromosome 13.[1 3] When the deletion is large there are usually associated congenital abnormalities, including severe mental retardation, and the patients do not reproduce. In patients with small deletions, however, the associated abnormalities may be less severe or absent[4] and offspring have roughly a 50% chance of inheriting the deletion and also developing the tumour.

Esterase D is found in most human tissues, but its function is unknown. The gene for esterase D has been localised to region 13q14[5] and patients with retinoblastoma carrying a deletion have 50% esterase D activity in their cells.[2] Determination of red blood cellular esterase D activities in a large population of patients with retinoblastoma led to the identification of patients with reduced enzyme activities, some of whom had not previously been diagnosed as patients with the deletion.[2] In this report we present details of one of these cases with a fairly small chromosome deletion that had escaped detection until measurements of esterase D were made.

Materials and methods

Chromosome analysis. Peripheral blood samples were obtained in heparinised tubes. 0·2 ml of blood was cultured in 5 ml of Roswell Park Memorial Institute medium supplemented with 20% newborn calf serum and 0·2 ml of phytohaemagglutinin (Wellcome, Beckenham, Kent) for 72 hours. After this time vinblastine sulphate (0·1 μg/ml) was added for 20 minutes and the cells harvested and treated with 0·07M potassium chloride for 10 minutes. Lymphocytes were then fixed in three changes of 3:1 methanol:acetic acid, and chromosome preparations were made using standard air drying techniques. Subsequent chromosome banding was performed by the modified trypsin-Giemsa method described by Cowell [6]

Enzyme analysis. Esterase D activities were measured in red blood cells essentially as described elsewhere.[2] The hydrolysis of 4-methylumbelliferyl acetate to 4-methylumbelliferone was followed fluorimetrically. Washed red cells were lysed by freezing/thawing and 10 μl of the lysate diluted 1:30

in 10mM sodium acetate pH 5·5. From this stock solution 10 μl was added to 2·98 ml of 10mM sodium acetate at 25°C and the reaction begun by the addition of 10 μl of 10mM 4-methylumbelliferyl acetate directly into the cuvette The increase in fluorescence was measured over two minutes using an excitation wavelength of 322 nm and an emission wavelength of 450 nm.

Haemoglobin concentrations were measured by diluting 50 μl of the original lysate 1·40 in neutral Drabkin's solution and reading the optical density at 415 nm. The enzyme activity was calculated as the relative production of 4-methylumbelliferone per gram of haemoglobin as described previously.[2]

Results

Case report. The patient, a boy, was born in 1982 at 36 weeks' gestation after a normal pregnancy and delivery. The head was large at birth with a circumference of 38 cm (over the 97th centile) and birth weight was 3400 g (50th centile) A squint was noticed at 10 months of age, darkening of the right iris at 1 year, and enlargement of the right eye at 13 months. At 16 months the diagnosis of right retinoblastoma was made and was immediately followed by enucleation. No abnormality of the left eye was found. Histopathological examination revealed a rosette forming retinoblastoma within the globe and no involvement of the cut end of the optic nerve At a recent examination, when the child was aged 3, there was no recurrence of tumour and the left eye remained normal

Psychomotor development was initially thought to be slow, but at 2 years the development quotient was 94. At 3 years the child was able to speak in sentences and was thought to be developing within the normal range.

Macrocephaly persisted from birth (at 3 years head circumference was 54·7 cm, which is above the 97th centile), while height and weight were still at the 50th centile. The head growth, however, remained parallel to the 97th centile from birth There were no other dysmorphic features The parents and an elder brother had no eye disorders. A recurrence risk of 2% for siblings and 6% for offspring was given at that time, based on estimations of Carlson and Desnick[7] and Fuhrman and Vogel.[8]

Chromosome and enzyme analysis
In December 1983 the karyotype analysis of the patient was reported as being normal Six months later the red cell esterase D value was shown to be 48% of normal activities, indicating deletion of one copy of the esterase D gene. Subsequent chromosome analysis revealed a small sub-band chromosome deletion (Fig. 1), tentatively described as 13q14·1-q14·3 Analysis of the parents showed no reduction in esterase D activities and no chromosome abnormality. The deletion in this instance thus represented a sporadic event. as is the case with the vast majority of 13q deletions associated with retinoblastoma.

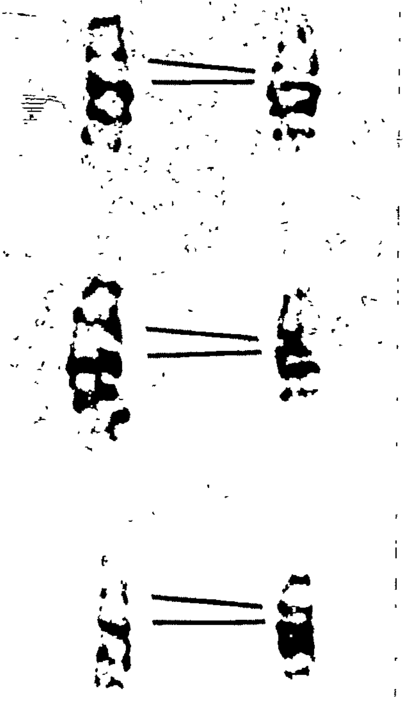

Figure *Chromosome 13 homologues from the patient showing a small sub-band deletion within region 13q14 The normal chromosome is shown on the left in each case and the deletion chromosome is on the right.*

Discussion

This report illustrates the importance of carrying out determinations of red cell esterase D routinely in patients with both unilateral and bilateral retinoblastoma because standard chromosome analysis is not always sufficiently sensitive for detection of small chromosome deletions The findings have serious implications for this patient as the true recurrence risk in his offspring is roughly 50% instead of the 6% quoted before the detection of the deletion

The importance of esterase D measurements was recently emphasised by Cowell *et al* where eight other deletions, four of which had not previously been recognised, were detected in a large series [2]

Contrary to a popular belief that it is only the cases with bilateral tumours that have a genetic origin, we have shown that 66% of deletion cases have unilateral tumours[2] In other instances chromosome deletions in the proband were inherited as a result of the deletion being carried in the form of a balanced chromosome translocation in one of the parents.[9–13] Thus it is important that the chromosomes of parents of patients with 13q deletions are also analysed In the case presented here the parents were karyotypically normal.

Small chromosome deletions in patients with retinoblastoma might be detected if they were analysed using high resolution chromosome banding techniques. Such methods are time consuming, often subjective, and technically difficult, however, in contrast to determinations of esterase D, which, although requiring more sophisticated machinery to carry out the tests, are reliable, quick, and easily subjected to quality control. One criticism of measurement of esterase D is that those deletions that do not include the esterase D locus will escape detection To date, however, only two such cases have been reported.[14 15] In these patients, whose esterase D activities were normal, the deletions must have involved a proximal breakpoint that occurred between the esterase D and retinoblastoma loci Both patients had characteristic dysmorphic features and severe mental retardation, however, which are usually associated with a chromosome deletion and would in themselves warrant chromosome analysis. It is important to note that patients with smaller chromosome deletions, such as the one reported here, are not always mentally retarded and also that not all mentally retarded patients with retinoblastoma have chromosome deletions. (Cowell JK. Manuscript in preparation.)

Over 90% of patients with retinoblastoma survive the tumour, although blindness often results. If the tumour presents in an advanced form the treatment involves the removal of the eye If this is not performed experience in the Third World, where treatment is minimal, has shown that the tumour will metastasise, usually down the optic nerve, and kill the patient. If tumours are detected early enough the consequences of the treatment may be less drastic. Cobalt implants, for example, often confine irradiation to the tumour and immediately adjacent areas and, depending on the site(s) of the tumour(s), vision may be only slightly impaired. Diagnosis of deletion carriers is often too late to help the affected individual as their deletions are only diagnosed at presentation One patient seen by our group recently had severe developmental delay and was subsequently diagnosed as a 13q deletion carrier as a result. (Fitzsimmons J. Personal communication) Frequent, detailed examination of the retinas allowed detection of the tumours at a very early stage, and treatment will probably be effective. For those patients diagnosed as deletion carriers at presentation the management of the tumour is no different from any other retinoblastoma. For the children of these patients, however, it will be possible to determine prenatally whether they have inherited the deletion and, if so, either the pregnancy could be terminated or special attention given to the child during the early months in an attempt to detect and treat the tumours at an early stage. Tumours rarely recur after 5 years.

We suggest, in conclusion, that determination of esterase D is a powerful diagnostic tool for the detection of chromosome deletions in chromosome region 13q14 and should be part of the routine tests performed on patients with retinoblastoma. The same samples used for determination of enzyme concentration can also be used for enzyme phenotyping, which, in the familial form of the tumour, can also be used for prenatal diagnosis.[16]

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Twenty five years ago

Purpura fulminans in a newborn baby

R L Van Der Horst (Durban)—Arch Dis Child 1962;**37**:436–41

An Indian male infant, the third child of healthy parents, was found to have several raised red patches on both arms, right thigh, and left cheek immediately after a normal birth at home. Over the next three days these lesions became dark blue in colour, increased in size, and blistered in the centre. After admission to hospital new lesions appeared and merged into one another, more bullae developed, and in some areas such as the buttocks the skin became thickened, hard, and necrotic. On the fourth day of life the left lower limb was cold and indurated It was purple in colour with a demarcation line above the ankle No peripheral pulses were palpable In spite of treatment with vitamin K and infusions of fibrinogen and fresh whole blood the infant's condition deteriorated with bleeding from nose and gums, the passage of tarry stools, and distension of the abdomen The positive laboratory findings included lowered plasma fibrinogen, thrombocytopenia, and haemoglobin concentration down to 5 6 g/dl Clot retraction was abnormal Death occurred on the eighth day. At autopsy widespread thrombosis was found in veins, capillaries, and arterioles There was extravasation of blood in the subcutaneous fat, large intestine, bladder, and perinephric fat All the intracranial venous sinuses were thrombosed

The author concluded that this disorder was essentially one of intravascular thrombosis. As the first child of the parents had died aged 9 days of a very similar illness the possibility of a genetically determined hereditary disorder was considered. From estimations of plasma fibrinogen concentrations in both parents (less than 40% of the mean) Van Der Horst suggested the presence of a congenital deficiency of fibrinogen in this family, although he seemed to consider that the cause of the purpura fulminans was more probably related to Shwartzman's phenomenon

Comment. This was the first recorded case of purpura fulminans in a newborn infant Several recent case reports have indicated, however, that the disease is a manifestation of disseminated intravascular coagulation and due to congenital absence of plasma protein C, which is one of the vitamin K dependent serine proteases In its activated form it is a potential anticoagulant as well as a profibrinolytic agent. The disease is inherited as an autosomal recessive Affected infants have protein C concentrations at zero, while in the heterozygous parents concentrations have been reported to be under 50% of normal. The cases so far reported have all ended fatally save for one Chinese infant in whom cryoprecipitate and fresh frozen plasma induced a remission that was successfully maintained by the administration of warfarin [1] It is important to recognise purpura fulminans in the newborn as a distinct entity, quite separate from the cases of fulminating or necrotic purpura that have been reported in older children. J H HUTCHISON

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Intensive consolidation chemotherapy for acute lymphoblastic leukaemia (UKALL X pilot study)

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SUMMARY Eighty two children with acute lymphoblastic leukaemia presenting at this hospital received one or two modules of intensive chemotherapy to consolidate remission. Modules were given after four and roughly 19 weeks on treatment. Each included two doses of daunorubicin (45 mg/m^2/day), cytosine arabinoside (100 mg/m^2 twice daily × 5), etoposide (100 mg/m^2/day×5), and 6-thioguanine (80 mg/m^2/day × 5). A total of 132 courses were given. This study included all new patients except girls aged 1–14 years with presenting leucocyte count $< 20\times10^9$/l. Twenty patients with recurrent disease were also included.

The first 32 patients were given cytosine as a 24 hour infusion, but combined with the other agents this was associated with severe intestinal toxicity, which necessitated a change to a less toxic 12 hourly bolus regimen. The complications of the module are reviewed in terms of myelosuppression, enterotoxicity, infection, and other clinical problems encountered. All patients became profoundly neutropenic and thrombocytopenic. The latter was significantly more severe after cytosine infusion. Overall, 64% received platelet transfusions and 85% were re-admitted with fevers requiring intravenous antibiotics for between four and 56 days. Gastrointestinal toxicity with the modified module occurred in 38% of patients and was severe in 13%.

This intensification module has been adopted by the Medical Research Council Working Party on Childhood Leukaemia for use in a multicentre study (UKALL X) and the details of the problems encountered in the pilot study may be of value to other centres now using this protocol.

Over 90% of children with acute lymphoblastic leukaemia will enter remission after treatment with vincristine, prednisolone, and asparaginase,[1] but a large number will subsequently relapse In 'good risk' girls with common acute lymphoblastic leukaemia and low presenting white blood cell count (WBC), long term survival of around 80% may be achieved.

For others, however, the outlook is less optimistic, and for boys with a high presenting WBC, long term survival is generally less than 40%

As in other childhood cancer the increased long term survival has accentuated the awareness of the long term side effects of chemoradiotherapy.[2] Clearer definition of prognostic factors using clinical, immunological, and cytogenetic characteristics may allow the selection of patients for whom less intensive treatment, with fewer long term side effects, is appropriate. The problem of how to improve survival in the intermediate and bad risk patients remains.

In the past few years a number of centres have studied the effect of additional agents given during the induction period.[3] Few have shown any clear benefit,[4 5] but many such regimens have been insufficiently intensive. Although not assessed prospectively, however, it seems likely that the multi-agent intensification by the BFM group has improved outcome.[6]

In the current Medical Research Council national trial (UKALL X) the possible advantages of similarly intensive consolidation therapy are being assessed in a randomised manner. A pilot study of a five day module, which comprised daunorubicin, cytosine arabinoside, 6-thioguanine, and etoposide (VP16–213)—'DATE'—incorporated after induction therapy, was started at this hospital in 1983. Here we report a prospective study of toxicity and supportive care after this module during the first 18 months of its use.

Patients

Between March 1983 and July 1984, 72 new cases of acute lymphoblastic leukaemia presented at this hospital Ages ranged from 1 month to 15 years, and 43 were girls. Thirteen had presenting white blood cell counts (WBC) $>100\times10^9$/l (six T cell, four null, and three common acute lymphoblastic leukaemia). With the exception of 23 'good risk' girls—who had WBC $<20\times10^9$/l, were aged 1–14 years, and were common acute lymphoblastic leukaemia antigen positive—who received standard induction and maintenance therapy, all patients were given either one or two intensive consolidation modules. Four patients with stage III mediastinal T cell lymphoma and 20 with relapsed acute lymphoblastic leukaemia were also included in the study Nine patients who started treatment before the start of the study were given the late module only (Table 1). In total 82 patients received 132 modules up to October 1984.

Methods

Details of the UKALL X pilot induction regimen are shown in Figure 1 and the consolidation module DATE in Figure 2 The first 25 patients were given cytosine as a continuous infusion over the five days, and all subsequent patients were given 12 hourly intravenous bolus injections

The elective times for early and late consolidation were at four and 19 weeks, respectively (Fig. 1). The late module was given after two months on maintenance chemotherapy, after cranial irradiation (18 Gy)—that is, roughly 15 weeks after the early module.

Seven patients were given the early module only. These comprised two children with presenting WBC 100×10^9/l who proceeded to bone marrow transplantation, one who died after the early module, two in whom the late module was cancelled due to the morbidity associated with the early module (both low presenting WBC), one girl with a borderline WBC (22×10^9/l), and one foreign patient in whom the late module was electively omitted.

Table 1 *Diagnoses of patients receiving DATE intensification and the respective numbers that were given single modules (early or late) or both early and late*

Diagnosis		*(n=)*	*Module timing*		
			Early	*Late*	*Both*
Acute lymphoblastic leukaemia	First remission	(58)	7	9	42
	Relapsed	(20)	11	—	9
T cell lymphoma		(4)	—	—	4

DATE comprised daunorubicin, cytosine arabinoside, 6-thioguanine, and etoposide

The first module was given early, at three weeks, in one child with recurrent disease who was slow to achieve remission The late module was given early in eight patients: four infants under 2 years who did not receive cranial irradiation and in whom irradiation was not repeated and the last module was given 8–12 weeks after the first, and one boy with a high presenting WBC who was not in complete remission at week 4 and was given the late module as soon as the blood count had recovered from the early module.

The early module was delayed in nine patients for the reasons listed in Table 2. The delay ranged from 1 to 8 weeks and in most cases was due to complications related to treatment during induction.

In 17 patients the late module was delayed more than 16 weeks after the first. In five this was due to

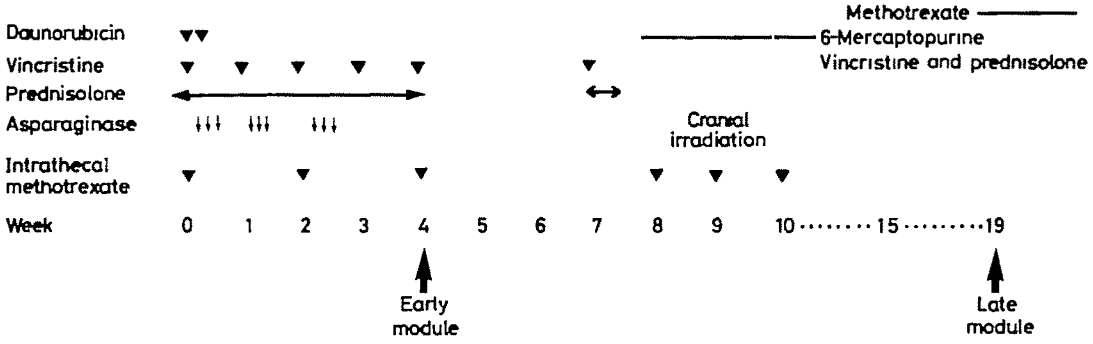

Fig 1 *Details of the drugs given and their timing, during induction, radiotherapy and early maintenance in UKALL X pilot protocol*

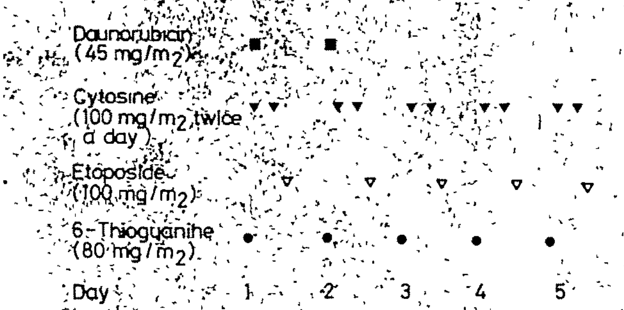

Fig. 2 *Details of the constituent drugs in the DATE intensification regimen. With the exception of 6-thioguanine (oral) all were given intravenously (see text for details).*

late cranial irradiation as a result of complications associated with the early module; in one irradiation was delayed for a short period until the child was 2 years old and then followed by the late module; in eight the delay was due to severe neutropenia related to intolerance of maintenance therapy started at the time of cranial irradiation; in one the delay was due to herpes zoster infection; and in two patients (both with low presenting WBC) the late module was delayed for one to two weeks for family reasons.

In all cases the blood count had recovered from previous treatment at the time of the module, with neutrophil count $>1\times10^9$/l, platelets $>100\times10^9$/l, and haemoglobin >8 g/dl. The patient's general condition, particularly in relation to nutrition and infection, was taken into account in deciding about the module timing and was balanced against prognostic factors such as age, sex, presenting WBC, and extramedullary disease at diagnosis.

Follow up and management of patients.

Blood counts and blood product support

Weekly blood counts were increased to daily once the platelet count had fallen to below 50×10^9/l, and platelet transfusions were given at below 20×10^9/l or if there was appreciable bleeding irrespective of count (four to five packs of platelets/m^2 daily was usually adequate). In ill or febrile patients platelets were given more readily (below 30×10^9/l) and more often because of their reduced effectiveness in such circumstances. Packed red blood cells were given if the haemaglobin concentration fell to below 8 g/dl. Granulocyte transfusions were considered only in patients with severe localised infection, such as cellulitis or abscess, or bacteriologically proven septicaemia not responding to appropriate treatment with antibiotics.

Management of infections

In view of the profound myelosuppression a high incidence of infectious complications were anticipated and at the start of the study all patients remained in hospital until the neutrophil count began to recover. Subsequently, all were allowed home after completion of chemotherapy, except infants in whom the signs of infection may be subtle, or where there was any doubt about parental ability to appreciate the need for early re-admission. Parents were advised to take the child's temperature if she or he appeared warm or in any way unwell. A temperature above 38°C was regarded as an indication to contact the hospital and usually led to re-admission. Oral decontamination of the bowel was not attempted, nor was protective isolation used.

The investigations carried out in the febrile neutropenic patients were as previously described,[7] with the addition of blood cultures in Sabauroud's medium, serial fungal serology, and viral culture and serology as clinically indicated. Stool samples were routinely screened twice weekly for conventional intestinal pathogens, and the identity and antibiogram of the aerobic Gram negative bowel flora were also determined. The results of the latter investigations were used to determine whether initial treatment with antibiotics should be the first or second line antibiotic policy of the unit. In the

Table 2 *Complications during induction chemotherapy in nine patients that led to delay in administration of early intensification The treatment given during the interim period is listed*

Case No	*Weeks' delay*	*Reason*	*Interim treatment*
1	1	Perforated appendix	Vincristine, prednisone
2	1	Leg abscess	Vincristine, prednisone
3	1	Septicaemia and diarrhoea	Vincristine, prednisone
4	1 5	Prolonged myelosuppression	Vincristine, prednisone
5	1	Diarrhoea, vomiting, and weight loss	Vincristine, prednisone
6	8	Wound infection and weight loss	Started maintenance
7	5	Acute epiglottitis and weight loss	Started maintenance
8	4	Encephalopathy and weight loss	Started maintenance
9	8	Septicaemia and malnourished	Started maintenance

absence of piperacillin resistant organisms piperacillin 300 mg/kg/day and gentamicin 8 mg/kg/day were used. When indicated by the antibiogram ceftazidime 50 mg/kg/day was substituted for piperacillin. Intravenous metronidazole was given to patients with severe diarrhoea Oral nystatin was routinely prescribed.

If the temperature settled promptly and no causative agent was found treatment with antibiotics was stopped when the child had been afebrile for 48 hours, irrespective of the blood count. Documented bacteraemia was followed by a 10 day course of appropriate treatment with antibiotics

In patients in whom fever failed to settle within five days of treatment with antibiotics, appropriate for cover of the aerobic Gram negative bowel flora, intravenous amphotericin was used Early treatment was influenced by the presence of candida in gut, mouth, or skin and was reviewed in the light of clinical response and serial candida serology estimated every three to five days. The duration of treatment with amphotericin was based on the documentation of presence or absence of systemic candida infection, which was indicated by a rise in antigen or antibody, or both. Where systemic sepsis was documented a course of six weeks' treatment was given. Where three serial estimations of antigen and antibody failed to reveal evidence of systemic disease treatment was stopped after two to three weeks or on recovery of the neutrophil count.

Enterotoxicity

As with suspected infection a low threshold for re-admission was maintained and parents were advised to contact the hospital in the event of any intestinal symptoms. If diarrhoea developed the child was re-admitted for observation and early intravenous fluids given if symptoms did not settle With severe enterotoxicity, parenteral nutrition was begun early, particularly in patients whose nutritional state was already suboptimal.

Results

As the amount of previous treatment might have influenced toxicity patients have been subdivided with regard to the timing of the module—that is, late module only, early module, or second module given to the same patient (repeat late module). The method of administration of cytosine is also considered and whether the patient was in first or subsequent remission. The times given refer to the number of days after starting the module. Statistical differences between groups were assessed using the χ^2 test.

Table 3 *Details of the myelosuppression after DATE* The incidence, onset, and duration are listed in relation to module timing, method of administration of cytosine arabinoside (I=infusion, B=bolus), and remission state*

	Cytosine arabinoside administration	*(n=)*	*Neutropenia (<0.5×10⁹/l)*					*Thrombocytopenia (<100×10⁹/l)*					*Anaemia (<8 g/dl)*		
			Incidence (%)	*Onset (days)*		*Duration (days)*		*Incidence (%)*	*Onset (days)*		*Duration (days)*		*Incidence (%)*	*Timing (days)*	
				Range	*Median*	*Range*	*Median*		*Range*	*Median*	*Range*	*Median*		*Range*	*Median*
First remission															
Late only	I	(9)	100	7–11	8	10–15	12	88	10–16	12	1–12	6	77	12–33	16
Early	I	(14)	100	6–11	9	6–15	9	92	8–17	11	1–7	2	69	7–19	13
	B	(39)	100	3–11	8	6–19	10	41	9–14	12	1–9	1	50	5–16	11
Repeat late	I	(7)	100	3–9	7	9–20	15	100	8–16	13	1–10	3	71	6–19	10
	B	(36)	100	3–12	8	8–15	12	68	9–17	12	1–12	1	48	8–30	10
Second remission															
Early	I	(11)	100	1–8	6	7–15	12	80	5–13	8	2–9	3	30	8–10	10
	B	(9)	100	3–12	7	9–14	11	50	8–17	11	1–2	1	89	5–13	11
Repeat	B	(7)	100	6–12	7	9–23	11	66	10–15	12	1–16	1	70	10–17	14
	I	(1)		6		40			9		30			6	

*DATE comprised daunorubicin, cytosine arabinoside, 6-thioguanine, and etoposide

Myelosuppresion. Profound myelosuppression was an invariable feature after treatment (Table 3). The neutrophil count fell to below $0{\cdot}5\times10^9/l$ in all patients and to undetectable numbers in most. The onset of neutropenia ranged from day 7–12 in new cases and 1–12 in patients with recurrent disease and the duration of neutropenia from 6–20 and 7–40 days, respectively. Severe thrombocytopenia occurred in many patients, the timing of onset ranging from day 5–17. Sixty four per cent of patients required platelet transfusions, and platelet requirements were higher in cases who had received cytosine as an infusion rather than as a bolus (88% *v* 56%, $p<0{\cdot}001$). Bruising and petechiae were not uncommon, but with the exception of intestinal haemorrhage in patients with severe enterotoxicity there were no serious bleeding problems. In three patients myelosuppression was particularly severe, lasting over three weeks. Two of these had recurrent disease and had been heavily pretreated. The other, a new case, developed severe enterotoxicity and septicaemia and, despite initial partial recovery of blood count, remained profoundly neutropenic and thrombocytopenic and developed candida septicaemia After eight weeks his count had completely recovered and he proceeded into maintenance therapy.

Enterotoxicity. This was graded according to severity (Table 4). The timing of onset of symptoms ranged from day 5–16 and their duration from 1–35 days (Table 4).

Characteristically, patients remained well during the administration of the module apart from some nausea and vomiting associated with daunorubicin. Cytosine was in general well-tolerated with no conjunctival, skin, or neurological reactions

The commonest intestinal symptom was abdominal pain, beginning a few days after completing treatment, although in some patients anorexia and vomiting were prominent. Pain was poorly localised, with few local signs Diarrhoea ranged from a couple of loose stools, settling after a day or two, to watery diarrhoea, passed several times a day associated with intermittent crampy abdominal pain. In severe cases, the stool was mucous or blood stained and complete casts of intestinal mucosal lining were occasionally passed in the stool. Abdominal distension was a common feature and was usually of gaseous origin compounded by some degree of ileus. Plain *x* ray film showed distended loops of small bowel, and in one case intramural gas was apparent. In severe cases ascites contributed to the distension, in part as a consequence of intestinal protein loss. Oral mucosal ulceration was rarely seen. When cytosine was given as a continuous infusion over five days 29% of patients developed severe grade III or IV enterotoxicity, and this contributed largely to the death of one child The administration of cytosine was therefore modified to a daily injection and this reduced the incidence of grade III or IV toxicity to 13% ($p<0{\cdot}001$). Moreover, with the bolus regimen, 60% had no intestinal symptoms compared with 24% after the infusion ($p<0{\cdot}001$).

Infection. Modules were followed by fever with neutropenia that required intravenous antibiotics in 85% of cases. The range of organisms isolated in blood cultures was similar to that previously reported from this unit,[7] with *Escherichia coli, Pseudomonas,* and *Staphylococcus epidermidis* or *Staph. aureus* predominating. The duration of treatment with antibiotics ranged from four to 25 days (median nine days). Several patients developed localised staphylococcal cellulitis, usually at an intravenous access site. One such patient, in whom

Table 4 *Onset, duration, and severity of enterotoxicity after DATE*

	Cytosine arabinoside administration	*(n=)*	*Onset (days)*		*Duration (days)*		*Toxicity grading*			*Requiring intravenous feeding*
			Range	*Median*	*Range*	*Median*	*0*	*I/II*	*III/IV*	
First remission										
Late only	I	(9)	6–16	11	2–10	3	1	6	2	1
Early	I	(14)	8–14	13	1–9	3	6	5	3	1
	B	(39)	3–9	6	2–15	7	21	8	8	4
Repeat late	I	(7)	5–13	9	2–14	6	0	4	3	1
	B	(36)	6–14	8	2–35	3	24	8	3	2
Second remission										
Early	I	(11)	5–16	10	2–15	4	4	4	3	3
	B	(9)	8–9	8	3–4	3	6	3	0	0
Repeat	B	(7)	9–10	9	9–10	9	4	3	0	0
	I	(1)	10		35				1	1

Intestinal toxicity grading I Occasional crampy pain, II Cramps and two to three loose motions each day, oral replacement, III Severe diarrhoea requiring intravenous fluids, IV Florid enterocolitis, usually requiring parentral feeding

Cytosine arabinoside administration I=infusion, B=bolus DATE comprised daunorubicin, cytosine arabinoside, 6-thioguanine, and etoposide blood cultures yielded positive results, received granulocyte transfusions. Six patients, four of whom had been given cytosine by infusion, received amphotericin because of unremittent fever, but in one case this was for severe candida oesophagitis. The duration of antifungal treatment ranged from five to 56 days (median 14 days) One fifth of the modules were followed by the use of intravenous metronidazole, mostly in the earlier patients in whom intestinal toxicity was more severe. Acyclovir was given in seven cases: in two as empirical treatment in unexplained encephalopathy but without firm supportive evidence for herpes infection, in one for severe facial herpes zoster, and in four for herpes simplex stomatitis.

Mortality. Two patients died after the unmodified module (infusion of cytosine) and one after the modified (bolus cytosine), an overall mortality of 3·6%. Both of the patients who died after the unmodified module had recurrent disease.

One girl, aged 13 years, with isolated central nervous system relapse, developed a fever on day 9, which persisted in hospital despite treatment with antibiotics. She died on day 11 with a fulminant *E. coli* septicaemia and intramesenteric haemorrhage.

A 4 year old girl, who had relapsed in the bone marrow on maintenance therapy, collapsed and died within a few hours of admission to her local hospital with a fever and mild diarrhoea that developed 48 hours after completing treatment. Although blood cultures yielded negative results, it was assumed this death was due to septicaemia. Postmortem examination revealed no specific cause and in particular no evidence of cardiomyopathy (she had received 315 mg/m^2 daunorubicin).

The child who died in first remission was a 2 year old girl with a presenting WBC of 231×10^9/l. She had a very stormy induction period, developing septicaemia and enterotoxicity, the latter probably due to the initial treatment with daunorubicin Because of these problems the early module was delayed until week 5. Despite this, she developed diarrhoea on day three of the module and died on day 15 with fulminant *Pseudomonas aeruginosa* septicaemia.

Discussion

As might be expected with any intensive combination chemotherapy regimen the morbidity associated with the DATE module was high. With the modified form, 85% of patients required readmission to hospital because of fever, and 13% developed severe enterotoxicity. In some patients abdominal pain was a major problem and, although moderate discomfort usually responded to simple analgesics or antispasmodics, opiates were required in severe cases, although given with caution where there was florid enterocolitis. In general no attempt was made to control diarrhoea with pharmacological agents. Most are ineffective in cytotoxic drug induced enteritis, although loperamide may have a role. The effect of this drug on gut motility may give rise, however, to misleading clinical signs, as in one child where an apparent improvement in diarrhoea after loperamide was followed by sudden massive loss of pooled fluid and profound hypokalaemia. Secondary clostridial infection should be anticipated and metronidazole or vancomycin may be indicated where there is a bloody diarrhoea. In severe cases the abdominal signs may resemble those of an 'acute surgical abdomen' with guarding and rebound tenderness, but there is rarely any indication for surgical intervention. The exception is clear radiological evidence of perforation where local repair may be possible or severe intestinal haemorrhage where resection of involved gut may be necessary.[8] Otherwise, laparotomy in these immunosuppressed, thrombocytopenic, and often septic children is likely to reveal an oedematous, haemorrhagic gut only, and the postoperative morbidity is high. Other, unrelated causes of an acute abdomen should also be borne in mind. In this series one child developed acute appendicitis in the week after treatment. Regular review by a paediatric surgeon with experience of oncology patients is necessary in an often delicate balance between timely or unnecessary intervention.

Cytosine has been implicated as a major cause of intestinal complications after combination chemotherapy.[9] As a single agent myelosuppression is usually the dose limiting factor,[10] but in combination with daunorubicin severe intestinal problems often arise.[11] As the DATE module has been designed for intermediate as well as high risk patients it was considered that severe toxicity in about one third of patients was unacceptable. The reduction in toxicity associated with the change from cytosine infusion to bolus is consistent with its short plasma half life.[12] This allows some recovery of intestinal crypt cells between doses. To what extent this modification alters therapeutic activity remains speculative, although there is some clinical evidence that cytosine infusion is more effective.[13]

Enteral feeding was invariably stopped during the acute phase as at this time there is usually severe villus atrophy.[9] During the recovery phase, however, energy supplemented, hypoallergenic diets may be useful in regrading to full oral feeds

Intravenous feeding was usually given using peripheral venous access. In a small number of patients central silastic lines were inserted percutaneously. In general central catheters such as Hickmann's catheters were not electively used and with the change from cytosine infusion the need for intravenous feeding diminished markedly.

In the ill patient close monitoring of electrolyte balance was essential as hyponatraemia, hypokalaemia, hypomagnesaemia, uraemia, and a variety of other abnormalities occurred. Metabolic derangements and renal dysfunction were often compounded by the effects of amphotericin and the aminoglycosides. Careful surveillance of blood concentrations of potentially nephrotoxic agents was clearly mandatory.

The early use of combined broad range antibiotics has reduced the mortality in patients with neutropenia.[15] The myelosuppression after DATE was severe, requiring close bacteriological surveillance and rapid treatment in the event of fever. When the period of neutropenia is particularly prolonged the risk of fungal infection is high and for this reason a low threshold for starting parenteral amphotericin B (the agent of choice[14]) is advisable.[15]

Although it is preferable to give early intensification soon after the blood count has recovered (particularly in patients with a poor prognosis), there may be clinical indications for some delay (Table 2). Such complications are not uncommon with current four drug induction regimens. Nutrition was a particular problem, and active measures should be taken to prevent excessive weight loss in patients who are ill during induction. Supplementary enteral feeds and early intravenous feeding may be needed before intensification treatment. With appropriate supportive care, the mortality of DATE should be low (≈2–3%), comparable with that for other similar intensification regimens.[4] The additional stress that such treatment puts on the families involved is clearly an important consideration and appropriate psychosocial support is needed. Only the current randomised Medical Research Council study will answer the question about whether the additional problems encountered by all concerned are justified by an improved prognosis.

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Malignant tumours in the neonate

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SUMMARY One hundred and two cases of neonatal cancers, representing 2% of all paediatric malignancies, were seen during a 60 year period at The Hospital for Sick Children, Toronto, Canada. The neonatal cancers included neuroblastoma (47%), retinoblastoma (17%), soft tissue sarcoma (12%), central nervous system tumours (9%), leukaemia (8%), and a few cases of Wilms' tumour, liver tumour, and miscellaneous tumours. The overall mortality from disease was 41%. Patients with retinoblastoma, Wilms' tumour, and neuroblastoma had the best prognosis. Forty three patients (42%) survived their neonatal cancers; all were treated with surgery or radiochemotherapy, or both, but none suffered long term major handicaps as a result of treatment. There was one instance of second malignancy of the thyroid gland induced by radiation. We conclude that although neonatal cancers are difficult management problems, many patients can be cured. Physicians should discuss with parents the possible risks associated with treatment before treatment is begun.

Cancer in the neonate is a rare event. Except for isolated case reports. there is little information on the prevalence, sites of origin, or tumour types encountered in this age group. Fraumeni and Miller, in a review of death certificates over a five year period in the United States, found the neonatal death rate from malignancies to be 1 per 6 24 million live births.[1] A study of mortality, however, does not represent the true prevalence as only certain malignancies are fatal Bader and Miller reported that the prevalence of cancer in the first month of life in the United States was 36·5 per million live births,[2] while Barson estimated the prevalence of congenital neoplasia to be 1/12 500 to 1/17 300 total births.[3] There are scant publications on the diagnosis and treatment of these patients, whose management poses unique problems.

We report the outcome of a group of 102 neonates found to have malignant diseases in a single institution over a 60 year period and their management problems.

Subjects and methods

The Hospital for Sick Children in Toronto, Canada, is the tertiary referral centre for most sick neonates and for paediatric malignancies seen in Ontario. During a 60 year period (1922–82), 5290 cases of paediatric malignancy were seen at the hospital, 102 of whom were neonates under 29 days of age. The tumour registry, the medical records, and the pathology registry were examined to determine the prevalence of paediatric malignancies. The clinical records of the patients were reviewed. Histological sections of biopsy specimens or autopsy material, or both, and bone marrow aspirates were available in all patients, except three cases of neuroblastoma with increased urinary catecholamines and two cases of soft tissue sarcoma, and were reviewed by all the authors except ANC to confirm the diagnosis of the malignancy.

Results

One hundred and two neonates were diagnosed as having malignancy in the first 29 days of life. Forty two patients presented on the first day, 13 during the next six days, and the remaining 30 between days 7 and 29. Sixteen diagnoses of neuroblastoma and one of Wilms' tumour were made incidentally at autopsy in neonates who died of unrelated medical problems. There were 64 boys and 38 girls, giving a sex prevalence of 1·7 1 Table 1 shows the prevalence of different cancers and the mortality from disease. Forty two neonates (41%) died from their malignancy, 43 (42%) survived, and 17 died of unrelated medical problems.

Neuroblastoma was the most common neonatal

Table 1 *Prevalence of different cancers and mortality in neonates presenting with malignant diseases*

Diagnosis	*Total No of cases (Ages 0–18 years)*	*No occurring in neonates*	*% Incidence in neonates*	*Mortality* from malignancy (No (%))*	*Long term survivors (No (%))*
Neuroblastoma	404	48	11.9	11*(23)	21†(44)
Retinoblastoma	148	17	11.5	4 (24)	13 (76)
Wilms' tumour	293	4	1.3	0*(0)	3 (75)
Liver tumour	56	1	1.8	1 (100)	0 (0)
Leukaemia	1609	8	0.5	8 (100)	0 (0)
Central nervous system tumour	917	9	1.0	8 (89)	1 (11)
Sarcoma	623	12	1.9	10 (83)	2 (17)
Miscellaneous tumours	1240	3	0.2	0 (0)	3 (100)
Total	5290	102	1.9	42 (41)	43 (42)

*Excluding 16 neonates with neuroblastoma in situ, one neonate with Wilms' tumour who died of unrelated medical problems, and one child with neuroblastoma who died at age 11 from a motor traffic accident

†Including the child with neuroblastoma who died, free of disease, at age 11 from a motor traffic accident

tumour in our series (48 cases) and represented 12% of all neuroblastomas seen. The boy:girl ratio was 2:1. Sixteen neonates had unsuspected neuroblastoma in situ within the adrenal glands that were discovered at autopsy after their deaths from unrelated medical problems. Thirty two patients presented with overt neuroblastoma. Fourteen patients had adrenal primary tumours, of which five were bilateral Seven patients had cervical tumours, eight had thoracoabdominal paraspinal tumours, and three had pelvic neuroblastomas. Two of the seven patients with cervical neuroblastoma presented with unilateral congenital Horner's syndrome. Three of the eight patients with thoracoabdominal paraspinal neuroblastoma had extradural extension of tumour into the spine. The prognosis was dependent on the stage of the disease. Death resulting from tumour occurred in none of the 16 patients with neuroblastoma in situ, in one of the 11 with stage I/II disease, in neither of the two with stage III disease, in four of the five with stage IV disease, and in six of the 14 with stage IV-S disease. Fifty five per cent of patients received treatment, which consisted of surgery or radiochemotherapy, or both. All of the 21 survivors received one or more treatment modalities. Of these 21 patients (median follow up 13 years, range 6–30 years), one boy had developed multifocal papillary carcinoma of the thyroid gland induced by radiation 18 years later, and another girl had died, in remission, of a motor traffic accident 10 years later.

Retinoblastoma, the next most common neonatal tumour, was diagnosed in 17 babies. Thirteen patients had bilateral tumours, while four had unilateral disease. Four patients were diagnosed at elective examinations of the eyes under anaesthesia performed because of a family history of retinoblastoma. The remaining 13 patients presented with strabismus, leucocoria, or heterochromia iridis Treatment consisted of enucleation or radiochemotherapy, or both Thirteen of the patients were long term survivors of retinoblastoma (median survival 6 years, range 2–35 years), and so far none have developed second malignancies.

Wilms' tumour was found in four patients. In two cases the mothers had colon and renal cell carcinoma, respectively. The two patients with bilateral disease presented at birth with bilateral abdominal masses. One patient died at 11 hours of age of hyaline membrane disease. The other patient had a left total and a right partial nephrectomy, abdominal irradiation, and chemotherapy He was alive and free of disease at 12 years The other two patients with unilateral stage I Wilms' tumours presented at weeks 3 and 4, with an abdominal mass and with haematuria, respectively. Both had surgery only and were free of disease at 14 and 10 years, respectively. All four cases of Wilms' tumour had favourable histology, but one of the patients with bilateral disease had focal dysplastic changes in the renal parenchyma.

One patient presented at birth with a fetal hepatoblastoma. He was treated with surgical resection, chemotherapy, and irradiation but died of brain metastases one year later.

The clinical information on eight neonates with leukaemia is shown in Table 2. Three patients had acute myelogenous leukaemia, one acute lymphoblastic leukaemia, and four acute undifferentiated leukaemia. All patients presented with anaemia, thrombocytopenia, high white blood cell counts, and organomegaly. One patient (case 8 in Table 2) also had meningeal leukaemia and leukaemic iritis, with leukaemic cells in the anterior chambers of his eyes at presentation. Four babies had leukaemic infiltration of the skin and two had testicular leukaemia at diagnosis. All eight died of their disease The four who received no chemotherapy

Table 2 *Clinical information on neonates with leukaemia*

Case No	*Sex*	*Presenting age*	*Diagnosis*	*Treatment*	*Outcome*
1	M	3 days	Acute undifferentiated leukaemia	None	Died, 1 month
2	M	Birth	Acute lymphoblastic leukaemia	Pred, VCR, Asp	Died, 15 months
3	F	Birth	Acute undifferentiated leukaemia	VCR, Cyclo, 6MP, Ara C	Died, 4 months
4	M	Birth	Acute myelogenous leukaemia (Down's syndrome with ventricular septal defect)	6MP, MTX	Died, 23 months
5	M	27 days	Acute myelogenous leukaemia	None	Died, 5 months
6	F	26 days	Acute myelogenous leukaemia	None	Died, 1 month
7	M	3 days	Acute undifferentiated leukaemia	None	Died, 35 days
8	M	Birth	Acute undifferentiated leukaemia	Pred, VCR, 6MP, MTX	Died, 24 months

Pred=Prednisone, VCR=Vincristine, Asp=L-Asparaginase, Cyclo=Cyclophosphamide, 6MP=Mercaptopurine, MTX=Methotrexate, Ara C=Cytosine arabinoside

died one to five months after diagnosis, and the four who received chemotherapy died four to 24 months after diagnosis.

Nine infants had malignant tumours that arose from the central nervous system (Table 3). The most common presenting feature was a rapidly enlarging head. Roughly half of the babies also developed vomiting or seizures. Most of the patients presented in the era before computed tomography and the diagnosis was made with ventriculography, arteriography, or air encephalography. Astrocytoma was the most common disease, all three cases being high grade tumours. There were two cases of primitive neuroectodermal tumour, one of medulloblastoma, one of ependymoma, and two of myxofibrosarcoma. The prognosis was poor, and only one patient remained alive beyond 2 years. Three patients had no treatment and died shortly after diagnosis. Five patients had radiotherapy or chemotherapy, or both, because their tumour could not be completely resected, and all five died of disease progression or complications of treatment. The patient who was alive, free of disease, and neurologically normal at 30 months after diagnosis had total resection of his frontoparietal myxofibrosarcoma, radiotherapy, and chemotherapy.

Twelve infants presented with soft tissue sarcomas in the neonatal period (Table 4). Eight patients had rhabdomyosarcoma, three had undifferentiated sarcoma, and one had leiomyosarcoma. Ten of the 12 babies died of their disease. The two long term survivors included a patient with leiomyosarcoma of the colon and a patient with an undifferentiated sarcoma of the orbit. It is of interest that both were cured by surgery alone.

The miscellaneous group comprised three patients

Table 3 *Clinical information on the nine neonates with brain tumours*

Case No	*Sex*	*Presenting age*	*Presenting features*	*Diagnosis*	*Treatment*	*Outcome*
1	F	Birth	Hydrocephalus, seizures	Cerebellar and cerebral primitive neuroectodermal tumour	Ventriculoperitoneal shunt	Died, 11 days
2	F	Birth	Large head	Left cerebral anaplastic astrocytoma	None	Died, 1 day
3	F	27 days	Hydrocephalus, vomiting	Ependymoma of fourth ventricle	Torkildsen shunt, partial resection	Died, 3½ months
4	M	20 days	Hydrocephalus, exophthalmus, seizures	Right cerebral astrocytoma	None	Died during air encephalogram
5	M	14 days	Large head, strabismus	Left frontal anaplastic astrocytoma	Surgery, chemotherapy	Died, 8 months
6	M	27 days	Vomiting large head	Cerebellar medulloblastoma	Partial resection, radiotherapy	Died, 2 months, of meningitis
7	F	27 days	Large head, hydrocephalus	Pineal primitive neuroectodermal tumour	Subtotal resection, ventriculoperitoneal shunt radiotherapy, intrathecal chemotherapy	Died, 4½ months
8	F	Birth	Occipital mass, vomiting	Posterior fossa myxofibrosarcoma	Subtotal resection, radiotherapy, chemotherapy	Died, 15 months
9	M	Birth	Left frontoparietal mass	Left temporoparietal myxofibrosarcoma	Total resection, radiotherapy, chemotherapy	Alive, 2½ years

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Table 4 *Clinical information on 12 infants presenting with soft tissue sarcomas in the neonatal period*

Case No	*Sex*	*Presenting age*	*Site*	*Diagnosis*	*Treatment*	*Outcome*
1	M	Birth	Colon	Leiomyosarcoma	Resection, colostomy	Alive at 13 years
2	M	Birth	Axilla	Embryonal rhabdomyosarcoma	Resection, radiotherapy	Died, 6 months, of metastases
3	F	Birth	Vagina	Rhabdomyosarcoma	Resection	Died, 16 months, of recurrence
4	M	Birth	Tongue	Rhabdomyosarcoma	Resection, irradiation using Tantalum implant	Died, 2½ years, of metastases
5	F	Birth	Vagina	Sarcoma botryoides	Resection	Died, 1 year of recurrence
6	F	Birth	Axilla	Undifferentiated sarcoma	Resection, radiotherapy, chemotherapy	Died, 3 months, of metastases
7	F	Birth	Foot	Alveolar rhabdomyosarcoma	Amputation, chemotherapy, radiotherapy	Died, 12 months, of metastases
8	F	5 days	Ulnar area	Aveolar rhabdomyosarcoma	Resection, radiotherapy	Died, 3 months, of metastases
9	M	7 days	Scalp and neck	Undifferentiated sarcoma	None	Died, 11 months, of metastases
10	M	14 days	Neck	Alveolar rhabdomyosarcoma	Resection	Died, 1 month, of metastases
11	M	14 days	Orbit and eyebrow	Undifferentiated sarcoma	Orbital exenteration	Alive, 18 years
12	M	28 days	Intradural spinal mass at T10-L2	Rhabdomyosarcoma	Resection	Died, 6 months, of disease

The first patient had a malignant schwannoma of the humeral area. He was alive and free of disease at 3 years after excision only. The second patient presented at birth with a large presacral mass. This was completely removed, and histology showed a benign sacrococcygeal teratoma with a malignant focus of embryonal carcinoma. She had adjuvant chemotherapy and was alive and free of disease at 21 months. The third patient had a testicular endodermal sinus tumour, which was resected, and was alive and free of disease at 43 years.

Discussion

Tumour masses are fairly common findings in the neonatal period but are rarely malignant. In our series malignant neonatal tumours comprised only 2% of all childhood malignancies The exact prevalence is difficult to determine, but in the United States it is reported to be in the region of 1 per 27 000 births.[2] In an average size maternity hospital one such patient would be born every nine years. Any experience in this must be gathered over a period of years from a large neonatal referral centre.

Forty one per cent of the tumours were evident on the first day of life, but 17% were only found at autopsy as an incidental finding. Thus the true prevalence may well be higher than the figures quoted, bearing in mind that many neonatal deaths do not undergo postmortem examination. Unlike other series, we found a male predominance, with a sex prevalence of 1·7:1. This was similar to but even more pronounced than the male predominance of 1·2.1 in all paediatric cancers.[4] Prenatal factors may play a part and affect one sex more than the other.

Like others,[5] we found no evidence of heredity in congenital malignancies, with the exception of four cases of familial retinoblastoma. Miller reported that certain childhood cancers were associated with congenital anomalies.[6] One might expect that this association would be more pronounced in congenital neoplasia. We only found one case of leukaemia associated with Down's syndrome and ventricular septal defect, a well known association.[7] Five patients with neuroblastoma had congenital heart disease, and one with neuroblastoma had multiple congenital abnormalities. There have been isolated reports describing the transplacental metastatic spread of cancer cells from mother to fetus in malignant melanoma,[8] leukaemia,[9] and choriocarcinoma.[10] We found no such instances in our series. We previously reported one baby with congenital neuroblastoma who had clumps of tumour cells in the fetal but not the maternal vascular channels of the placenta.[11] There was no evidence of transplacental spread of cancer from the child to the mother in this or in other reports.[12] Two mothers with recently diagnosed malignancies, colon and renal cell carcinoma, respectively, both gave birth to babies with congenital Wilms' tumour. We found no previous reports of similar associations and there was no evidence of maternal exposure to drugs or carcinogens that could have accounted for either the maternal or the neonatal tumours. Similarly, there was no history of maternal ingestion of alcohol or hydantoin anticonvulsants[13 14] in any of our cases of neonatal neuroblastoma or Wilms' tumour.

The treatment of neonatal cancer poses major management problems. Some lesions, like hemangioendothelioma of the liver, are of borderline malignant potential, while others, like neuroblastoma, may sometimes undergo spontaneous regression.[15] In the acute clinical setting the biological behaviour of the tumour is often unpredictable, and the management of the patient can be controversial. This controversy is particularly common in cases of congenital neuroblastoma where death can occur from complications related to either treatment or disease.[16]

The use of chemotherapy in neonates is associated with a higher incidence of immediate complications, especially infections,[17] and chemotherapy can potentially affect the child's subsequent development. Radiotherapy, especially to immature tissues such as brain. lung, liver, kidney, and bone, can lead to major handicaps in survivors.[18] The review of our 43 long term survivors has not shown severe physical or mental disabilities. Irradiation is also implicated in the development of second malignancies.[19] Patients of all ages are at risk, but there is no evidence that younger children and neonates are especially vulnerable.[18] They are, however, at risk for many more years than adults who received similar treatment Li and coworkers calculated that there is a 12% cumulative probability of developing a second cancer in an irradiated field in patients of all ages who survived five years or more after their first cancer.[19] So far, in 43 long term survivors of neonatal cancer we have documented only one case of thyroid carcinoma, which developed in an irradiated field. In patients with hereditary retinoblastoma who have a predisposing genetic risk for cancer the computed risk of second malignancies is considerable.[20]

We conclude that although neonatal malignancy is rare, a large percentage of the patients can be successfully treated and cured with little impairment to future well being. As the management of these patients poses great demands on both the parents and the physicians any proposed treatment and the risks should be thoroughly discussed with the parents before it is implemented.

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Influence of elective preterm delivery on birthweight and head circumference standards

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SUMMARY. We calculated new birthweight and head circumference centiles for boys and girls between 24 and 42 weeks' gestation from 20 713 singleton live births at our hospital between 1978 and 1984. Among the 803 babies born at or before 34 weeks' gestation, 28% were delivered electively for fetal problems; they were considerably lighter than babies born after spontaneous preterm labour. In contrast, they showed only a small deficit in head circumference, possibly due to a brain sparing effect in growth retarded infants. Electively delivered preterm infants cause a bias in birthweight and head circumference centiles and we recommend that these babies should be excluded when these centiles are calculated.

Commonly used tables of birthweight and head circumference centiles[1–5] differ from one another, varying both in the mean and spread of values at different gestational ages. These differences are likely to reflect differing degrees of accuracy in determining gestational age but also genuine differences in the populations from which the data were derived A further problem is the lack of data relating to very early gestational ages, yet elective delivery of infants before 30 weeks' gestation is increasingly common.

Thus there is an incentive to construct new standards based on local data, and such data will become more widely available as more hospitals develop computerised obstetric data banks. In constructing centiles based on deliveries at our hospital between 1978 and 1984 we noticed that the birth weights of our preterm babies were lower than those reported in other series based on births occurring 10 or 20 years earlier. We surmised that this might be due to the fairly large number of preterm infants in our series delivered electively for fetal problems. We therefore decided to examine separately the birth weights and head circumferences of electively delivered preterm babies and those born after spontaneous onset of labour.

Patients and methods

Detailed and complete information about all deliveries at the John Radcliffe Hospital, Oxford, has been recorded on the Oxford Obstetric Data System since 1978. Coding is from the case notes taken by trained staff, with supervision throughout by one of us (CWGR). The data are double keyed and subjected to rigorous error checks (full details on request)

The system provided the birth weights and gestational ages of 20 713 singleton infants, comprising all those births in 1978–81 and births at 34 weeks' gestation or less in 1982–84 Of these infants, 19 107 (92%) also had a recorded occipitofrontal head circumference. Nearly all (96%) were white. Study infants were selected after excluding stillbirths and babies with major congenital malformations—that is, defects of the skull, brain, spinal cord, musculoskeletal system, and chromosomes and renal agenesis.

Healthy babies were weighed in the delivery suite and those needing special care on admission to the special care nursery From 1978 to 1981 we used scales (Avery) accurate to within 5g, which were subjected to weekly validation. During 1981 these were replaced by electronic scales (K-Tron) accurate to within 1g, which were also regularly validated. Head circumference was measured by a paediatrician within 24 hours of birth, using a disposable tape.

Gestational age was defined as the number of completed weeks from the last menstrual period. This result was compared with gestational age predicted by an early—that is, before 20 weeks—ultrasound scan. As the approximate 95% confidence limits for this prediction are ±10 days,[6] the scan assessment was preferred only if it estimated a gestational age differing by more than 14 days from the estimate based on dates. Assessment of gestational age by paediatric examination[7] was made for low birthweight (<2000 g) babies If the assessment by paediatric examination differed by more than 21 days from the previously estimated gestational age the former was preferred.

Ultrasound scanning before 20 weeks' gestation was carried out on an estimated quarter of all women in 1978, the proportion rising steadily to half of all women in 1984. For the remaining women, gestational age was estimated from dates and paediatric assessment alone. Where gestation estimated by dates was clearly incompatible with the size of the baby, or where the date of the last menstrual period was unknown, the baby was excluded from our series; 169 babies (0·8% of the total) were excluded for this reason

Birthweight and head circumference means and standard deviations were calculated separately for boys and girls for each week of gestational age.

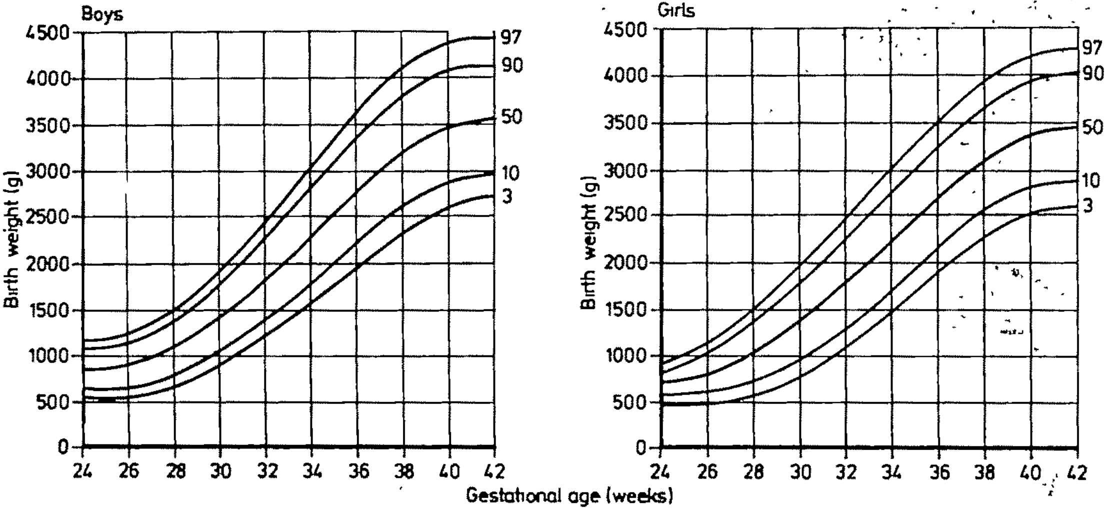

Fig 1 *Birthweight centiles for all the babies studied*

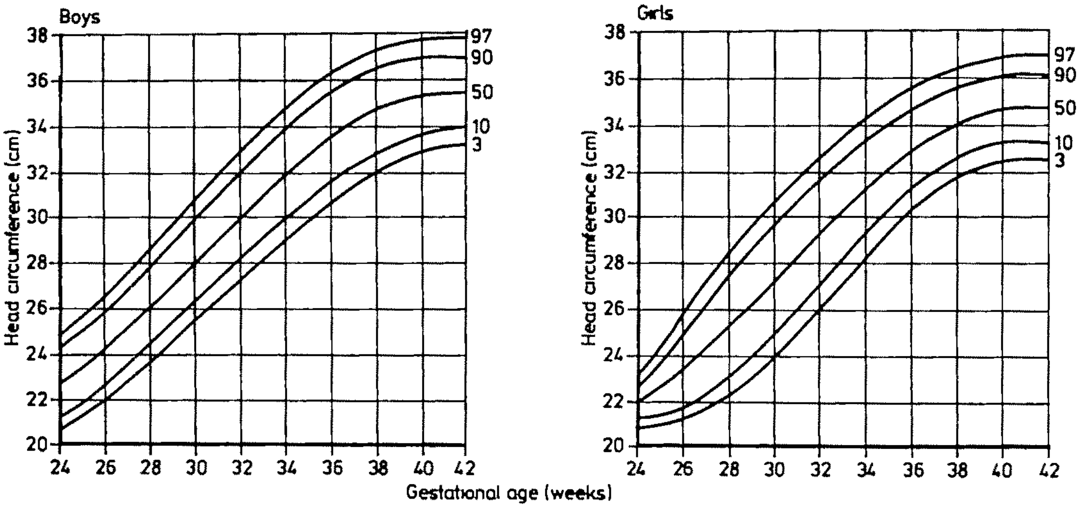

Fig. 2 *Head circumference centiles for all the babies studied*

Curves were fitted to the mean values, using polynomial regression, the best fit (r=0·99) being obtained with a third degree polynomial.

The 803 babies of gestational age 34 weeks or less were separated into two groups, 'elective' and 'spontaneous'. The 'elective' group (n=226) included all babies born after induction of labour or by caesarean section before labour for pre-eclampsia, intrauterine growth retardation, fetal distress, or rhesus incompatibility. The 'spontaneous' group (n=577) consisted of babies born after spontaneous premature labour, premature rupture of the membranes, or antepartum haemorrhage. Birthweight and head circumference means and standard deviations were calculated between 24 and 34 weeks' gestation for the spontaneous group and between 27 and 34 weeks' gestation for the elective group. Only four babies were delivered electively before 27 weeks and they were excluded.

To examine the influence of the electively delivered preterm babies on the birthweight and head circumference standards, a second set of curves was constructed excluding these babies. These curves were fitted, using polynomial regression, to the mean values for the spontaneous group between 24 and 34 weeks' gestation and the mean values for all babies at later gestations.

Comparisons between means were made using the *t* test, correction for unequal variances followed the method of Cochran.[8]

Results

Preliminary analysis. The distributions of birth weight and head circumference at each gestational age were examined. Before 32 weeks' gestation there were too few observations to give a clear picture. At 32 and 33 weeks' gestation both distributions showed a negative skew, which was reduced by removing data from the electively delivered babies. At later gestational ages the distributions were very close to normal. Based on these observations and supported by data from other studies,[3 4 9] the centiles at all gestational ages were estimated assuming a normal distribution. The 3rd and 97th centiles were placed 1·88 SD from the raw mean and the 10th and 90th centiles 1·28 SD from the mean. The resulting centiles were smoothed using polynomial regression.

Birthweight and head circumference values. Smoothed means and centiles of birth weight and head circumference for all babies of gestational age 24 to 42 weeks are illustrated in Figures 1 and 2. Smoothed mean values for boys were higher than for girls at each week of gestational age. Head circumference values were more closely clustered around the mean than were birthweight values.

Raw birthweight means for the spontaneous and elective groups between 27 and 34 weeks' gestation are shown in Table 1 and raw head circumference means in Table 2. At each gestational age, babies in the spontaneous group were heavier and had larger heads than those in the elective group. The differences in mean birth weight ranged from 163 to 569 g and were significant except at 28 weeks' gestation in boys. The differences in head circumference were proportionately smaller (ranging from 0·8 to 4·1 cm)

Table 1 *Birthweight raw means for the spontaneous and elective groups by gestational age*

Gestational age (wks)	*Spontaneous*		*Elective*		*p Value*
	n	*Mean (SD) (g)*	*n*	*Mean (SD) (g)*	
Boys					
27	17	1085 (167)	3	690 (50)	<0·001
28	14	1122 (133)	5	903 (269)	NS
29	23	1310 (201)	13	968 (228)	<0·001
30	18	1467 (247)	13	1168 (253)	<0·01
31	23	1751 (290)	7	1304 (338)	<0·05
32	48	1965 (249)	9	1541 (361)	<0·01
33	66	2078 (279)	30	1915 (390)	<0·05
34	94	2363 (345)	28	1935 (445)	<0·001
Girls					
27	12	1009 (221)	3	605 (151)	<0·05
28	20	1101 (167)	6	789 (108)	<0·01
29	17	1410 (151)	6	841 (269)	<0·01
30	6	1566 (270)	13	1078 (308)	<0·05
31	17	1653 (337)	15	1211 (315)	<0·01
32	20	1722 (270)	14	1469 (380)	<0·05
33	33	2071 (306)	31	1818 (365)	<0·01
34	98	2330 (336)	26	1828 (315)	<0·001

NS=Not significant

Table 2 *Head circumference raw means for the spontaneous and elective groups by gestational age*

Gestational age (wks)	*Spontaneous*		*Elective*		*p Value*
	n	*Mean (SD) (cm)*	*n*	*Mean (SD) (cm)*	
Boys					
27	16	25·6 (1·23)	3	23·2 (0·64)	<0·01
28	12	26·3 (1·12)	5	24·8 (1·46)	<0·05
29	21	27·5 (1·72)	10	25·9 (1·47)	<0·05
30	16	28·1 (1·39)	12	27·3 (1·59)	NS
31	22	29·1 (1·65)	7	28·3 (1·53)	NS
32	43	30·6 (1·39)	9	28·8 (1·60)	<0·001
33	64	31·5 (1·48)	26	30·7 (1·94)	<0·05
34	89	32·2 (1·40)	26	31·1 (1·59)	<0·001
Girls					
27	11	25·8 (1·27)	3	22·3 (1·70)	NS
28	17	25·8 (1·65)	6	24·6 (1·56)	NS
29	13	28·2 (1·37)	5	24·1 (1·87)	<0·01
30	6	28·6 (1·63)	13	26·0 (1·42)	<0·01
31	17	28·9 (1·79)	14	27·6 (1·65)	<0·05
32	15	29·3 (1·77)	13	28·5 (1·35)	NS
33	31	31·2 (1·51)	30	30·5 (1·45)	<0·05
34	96	32·0 (1·33)	23	31·0 (1·49)	<0·01

NS=Not significant

and not all were significant. Smoothed mean values of birth weight and head circumference for the spontaneous and elective groups are illustrated in Figures 3 and 4.

The effect of the electively delivered preterm babies on the birthweight and head circumference mean curves is shown in Table 3. Between 26 and 34 weeks' gestation smoothed mean birth weight excluding these babies was higher than the smoothed mean based on all the babies. The difference was most pronounced between 28 and 32 weeks' gestation, being 80 to 100 g for boys and 140 to 160 g for girls. There was little difference, however, between the head circumference mean curve based on the spontaneous group and that based on all the babies. The maximum differences (0·3 to 0·4 cm for boys and 0·8 to 1·0 cm for girls) were observed between 27 and 32 weeks' gestation. The spread of birth weights (assessed by variance) was smaller among the spontaneous group alone than among all the

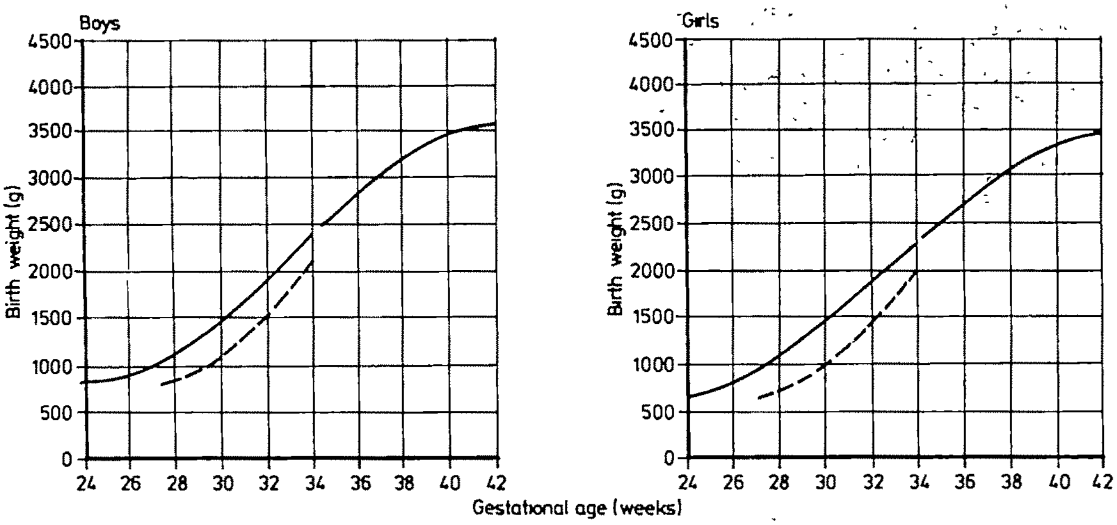

Fig 3 *Smoothed mean values for birth weight in the spontaneous (——) and elective (– – –) groups up to 34 weeks' gestation and in all the babies at 35 weeks' gestation and later*

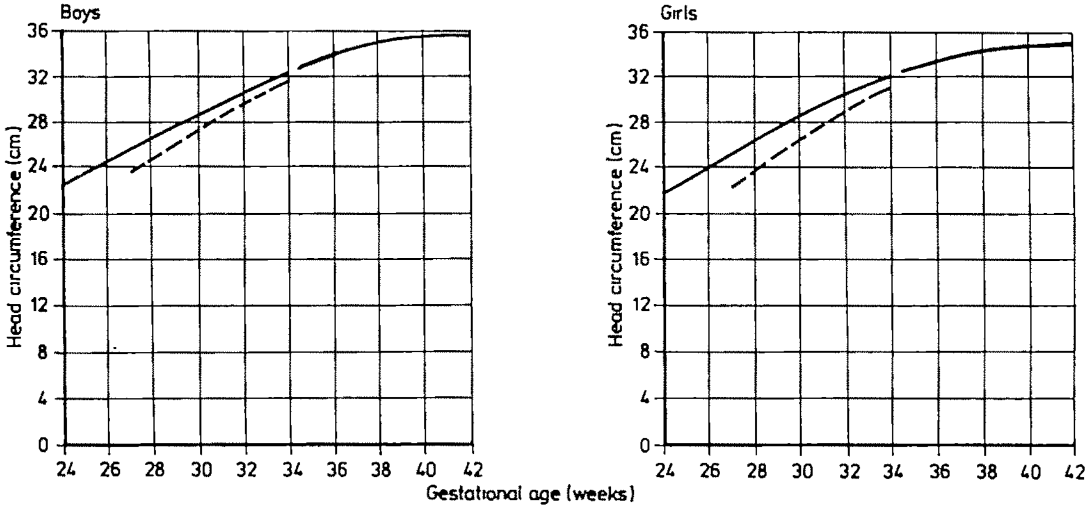

Fig 4 *Smoothed mean values for head circumference in the spontaneous (——) and elective (– – –) groups up to 34 weeks' gestation and in all the babies at 35 weeks' gestation and later*

Table 3 *Birthweight and head circumference smoothed means for all babies and for the spontaneous group only*

Gestational age (wks)	*Birthweight (g)*		*Head circumference (cm)*	
	All babies	*Spontaneous group*	*All babies*	*Spontaneous group*
Boys				
24	820	820	22·7	22·6
25	840	840	23·5	23·6
26	850	900	24·3	24·5
27	930	1000	25·2	25·5
28	1050	1140	26·2	26·5
29	1210	1310	27·1	27·5
30	1400	1500	28·1	28·5
31	1620	1710	29·1	29·5
32	1850	1930	30·1	30·4
33	2090	2160	31·0	31·3
34	2330	2390	31·9	32·1
Girls				
24	670	670	22·0	21·6
25	710	740	22·7	22·8
26	780	840	23·5	24·0
27	860	970	24·4	25·2
28	980	1120	25·3	26·2
29	1130	1290	26·3	27·3
30	1320	1480	27·4	28·3
31	1530	1690	28·4	29·3
32	1760	1910	29·4	30·2
33	1990	2110	30·4	31·0
34	2230	2330	31·3	31·7

babies, although the differences in variances did not in general reach significance. The same tendency was observed for head circumference (variances not shown in Table 3).

Discussion

Among babies born at a gestational age of 34 weeks or less we have observed that those born after spontaneous onset of labour are considerably heavier and have slightly larger head circumferences than those delivered electively. This is not surprising as most elective deliveries are because of severe pre-eclampsia, suspected intrauterine growth retardation, or fetal distress, all of which are known to be associated with unusually small fetal size. Between 27 and 34 weeks' gestation, nearly 30% of babies in our series were delivered electively. Inclusion of these babies in our calculations resulted both in lower mean birth weight and in greater variation of birth weight than would otherwise have been obtained. Their effect on head circumference values was, however, slight, perhaps due to a brain sparing effect in growth retarded babies.

It is generally supposed that birthweight and head circumference standards should reflect the ideal values for sex and gestational age. For this reason, published standards usually exclude stillbirths[1 3–5 10] and babies with serious congenital abnormalities,[1 2 4 5 9] with hydrops, or born to diabetic mothers.[1 4 5 9] It therefore seems logical to exclude babies born after other complications known to affect fetal size, such as pre-eclampsia or placental insufficiency. Exclusion of abnormal babies from the calculation of birthweight and head circumference standards results, however, in a paradox. The standards represent the population of normal babies, and yet a baby whose measurement is found to fall outside the cut off centile will be defined as abnormally grown. Furthermore, the exclusion of abnormal babies from the standards will narrow the spread of values observed at any gestational age, so that the measurement of any individual baby will be more likely to fall outside a given centile.

There is a case, though, for excluding particular abnormalities from the standards, while including others. The infants to be included should match the population to which the standards will be applied. For instance, if there is no intention of estimating the birthweight or head circumference centiles for macerated stillbirths or for grossly malformed infants these infants should not contribute to the standards. This argument could leave other abnormal infants, such as those born to diabetic or pre-eclamptic mothers, in the calculation of the standards.

Conceptual arguments about the inclusion or exclusion of particular abnormalities from birthweight and head circumference centiles will not matter in practice if the abnormality is rare enough not to affect the means or standard deviations observed at any particular gestation We have shown, however, that the growth retardation associated with elective preterm delivery occurs often enough to affect both the mean and spread of birth weight and, to a lesser extent, of head circumference at a gestational age 34 weeks and earlier.

The proportion of electively delivered preterm babies in the birthweight and head circumference series of the 1960s and earlier is not recorded. It is certain, though, that elective preterm delivery has increased in the last 10 or 15 years. Obstetricians are now better able to diagnose impending intrauterine death and, because of the improved survival of preterm babies, are more willing than before to deliver them electively for problems such as pre-eclampsia. Many of these pregnancies would previously have resulted in stillbirth, though there would have been some live births at a later gestation. This change in obstetric management will have produced an 'artificial' excess of small preterm live births and would account for the negative skew we observed in the birthweight and head circumference distributions at 32 and 33 weeks's gestation. This skewing is reduced by the removal of electively delivered infants, leaving roughly normal distributions similar to those observed at later gestational ages.

As it is illogical that changes in obstetric practice should alter the definition of an abnormally grown baby and as we cannot determine the 'correct' frequency of the electively delivered preterm infants at each gestation, we suggest that they should be excluded from birthweight and head circumference standards. The proposed standards would be based on the spontaneous group of births between 24 and 34 weeks' gestation and on all births at later gestations. The separation of elective and spontaneous births only up to 34 weeks' gestation is to some extent artificial and we recognise that our recommendation is a compromise. The distorting effect of elective deliveries is likely to occur at later gestations also, but the effect would be expected to decrease sharply towards term as the proportion of elective deliveries in the population declines. Whether or not birthweight standards should be adjusted for elective deliveries beyond 34 weeks' gestation is a subject for further study.

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Periventricular leucomalacia and neurodevelopmental outcome in preterm infants

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SUMMARY During an 18 month period, 120 preterm infants of 34 weeks' gestation or less were prospectively examined for periventricular leucomalacia (PVL) by cerebral ultrasound. Neurological and developmental assessment was carried out at 18 months of age corrected for prematurity in 82 surviving neonates. The developmental outcome (Griffiths development quotient) was above 80 and similar in infants with normal scans (n=41), isolated periventricular-intraventricular haemorrhage (n=13), and post-haemorrhagic hydrocephalus (n=4), and no major handicap was diagnosed in these groups. By contrast, the prognosis was variable and poorer in infants with PVL (n=24) and depended on the extent and site of the lesion. Infants with frontal PVL (n=13) developed normally. Major sequelae (n=8) were closely related to frontal-parietal PVL and frontal-parietal-occipital PVL and could be ascribed to the presence of cysts as well as to a persistent hyperechogenic ultrasonographic PVL appearance. A relation between size and site of the lesion and type and severity of the handicap was established.

Brain ultrasonography is used extensively for the detection of cerebral lesions in the newborn. Its validity for the diagnosis of periventricular leucomalacia (PVL) has been debated.[1–3] Based on correlative studies between ultrasound appearances and postmortem observations, it is clear that accurate identification of PVL can be achieved.[4 5] None the less, the precise predictive value of brain ultrasonography in the diagnosis of PVL is unclear[6 7]

The main purpose of this study was to describe prospectively the type, site, and extent of PVL and to evaluate the neurodevelopmental outcome of children with PVL at 18 months of age compared with children with normal scans or with periventricular-intraventricular haemorrhage (PVH).

Patients and methods

A total of 120 infants of 34 weeks' gestation or less were scanned in the neonatal unit of this hospital. Twenty two died in the neonatal period (seven with normal scans, nine with PVH, five with PVL, and one with cerebral malformation). Sixteen were lost to follow up (13 with normal scans, one with meningitis, and two with PVH). The remaining 82 patients were grouped according to ultrasound diagnosis and followed up to 18 months of age. Group A (n=24) comprised infants with PVL with or without PVH, group B (n=41) infants with normal scans, group C (n=13) infants with isolated PVH without PVL or ventricular dilatation, 10 of whom had subependymal haemorrhage and three intraventricular haemorrhage, and group D (n=4) infants with arrested or progressive post-haemorrhagic obstructive hydrocephalus without PVL.

Included among the survivors were all but one of 54 children who were the subjects of a previous report that addressed outcome up to 12 months of age.[8] The child not included was disregarded because of the omission of regular sequential scanning. There was no change in the interpretation of brain scans from the original report.

The birth weight, gestational age, sex distribution, and ultrasonographic appearances in the four groups are shown in Table 1.

Ultrasound scans. Infants were prospectively scanned with an American Technical Laboratories mechanical sector scanner and 7·5 MHz transducer. Scanning was performed through the anterior fontanelle in the coronal and parasagittal planes as soon

Table 1 *Neonatal data according to brain ultrasound findings in the four groups*

	Group			
	A (n=24)	*B (n=41)*	*C (n=13)*	*D (n=4)*
Mean (SD) birth weight (g)	1262·7 (298)	1554 (384)	1542 (402)	1520 (317)
Mean (SD) gestational age (weeks)	29·9 (1·8)	31·9 (1·5)	31·5 (1·5)	31·5 (1·9)
Sex (M:F)	10:14	20:21	4:9	2:2
Main ultrasonographic diagnosis	PVL and PVH grades I (n=7), II (n=10), and III (n=1), and, no PVH (n=6)	Normal scans	PVH grades I (n=10) and II (n=3)	2 arrested hydrocephalus and 2 progressive hydrocephalus (shunted)

PVL=Periventricular leucomalacia; PVH=Periventricular-intraventricular haemorrhage.

as the infant was admitted, daily during the first week of life and thereafter once weekly or more if necessary until discharge from hospital.

Ultrasound definitions and classifications, as well as diagnostic methodology, remained uniform throughout the 18 months. The degree of severity of PVH was defined according to the three grading system of Levene.[9] The size of the ventricles was measured and related to the centile chart[10] and the pattern of dilatation was described separately (transient, arrested, or shunted). If the measurement was greater than two standard deviations from the mean ventricular dilatation was diagnosed. The diagnosis of hydrocephalus was made when shunting was required or when the size of the ventricles remained markedly enlarged, well above two standard deviations.

PVL was defined in two stages. The early stage occurred within the first days of life and consisted of a characteristic triangular increased echogenicity visible for at least several consecutive days in both coronal and parasagittal planes in the vicinity of the external angles of the lateral ventricles in the periventricular white matter. The late stage was observed from the second to the 10–12th week of life and consisted of areas of reduced echogenicity, resolving progressively into cystic cavitation.[4]

Ultrasound changes described in the survivors were consistent with the diagnosis of PVL as they were similar to ultrasound scans of infants whose diagnosis was confirmed at postmortem examination. Doubtful or transient increased echogenicity and a posterior periventricular halo[11] were not considered as definite PVL, and these infants were classified for the follow up in the normal group or PVH group, depending on the other ultrasonographic appearances.

The size and site of PVL changes were described separately and defined as frontal leucomalacia when frontal areas only were involved (Fig. 1), frontal-parietal leucomalacia when frontal-parietal areas were affected (Fig. 2), and frontal-parietal-occipital leucomalacia in cases of extensive lesions involving the entire periventricular white matter from anterior to the frontal horns and from posterior to the occipital horns (Fig. 3).

Neurological assessment and follow up. Gestational age was determined from maternal dates and Dubowitz scores.[12] The babies were then examined by staff not involved in the neonatal care at ages corrected for prematurity of 3, 6, 9, 12, and 18 months. The follow up examination consisted of a detailed neurological examination,[13 14] an assess-

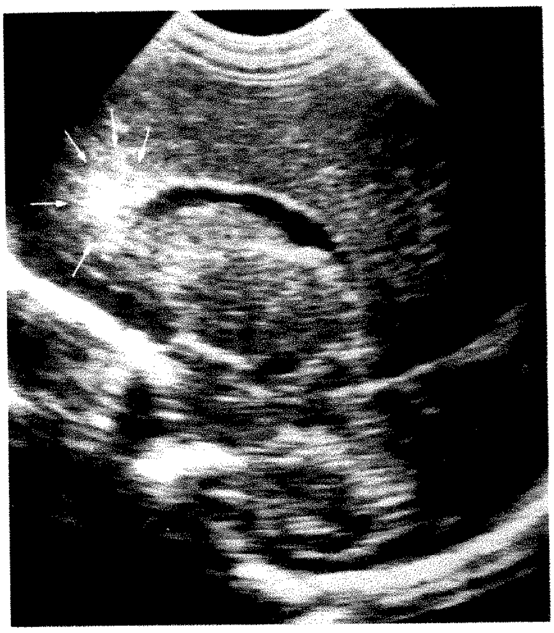

Fig. 1 *Parasagittal ultrasound scan, showing a focal increased echogenicity located anteriorly to the frontal horns of the lateral ventricles. This lesion evolved into cystic formation within two weeks.*

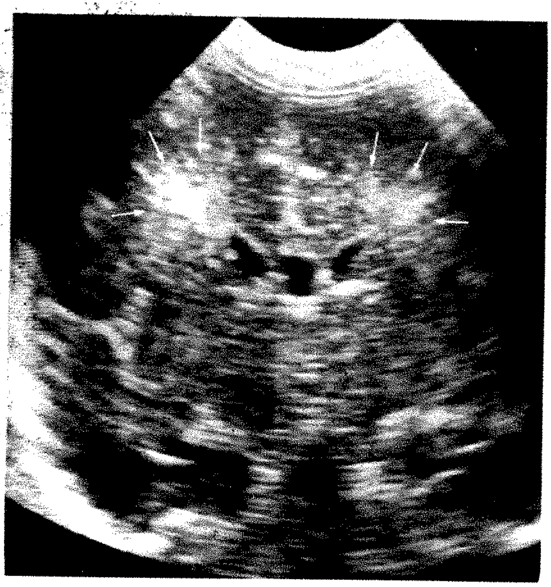

Fig. 2 *Coronal ultrasound scan of the middle fossa, showing a characteristic triangular increased echogenicity involving the parietal areas. Subsequent development of cysts was noted.*

ment of development using the Griffiths scale,[15] and an evaluation of vision and hearing according to the Stycar method.[16,17] Children were regularly examined by an ophthalmologist and if necessary referred for audiometric assessment (auditory brain stem response and audiometry).

Neurological outcome was classified as normal or as major handicap (spastic diplegia, quadriplegia, hemiplegia, severe auditory and visual impairment, and developmental delay (developmental quotient (DQ) <80)).

Results

Neurodevelopmental outcome in relation to ultrasonographic diagnosis. The overall incidence of major handicaps was 9·7%. The mean (SD) DQ was 88 (21·3) in group A, where lesions of PVL were diagnosed. Eight of the 24 children had a major handicap (three had cerebral palsy, one mental retardation, and four multiple handicaps). By contrast all children in groups B, C, and D had a DQ>80, and no child had a major handicap. The mean (SD) DQs in groups B, C, and D were 99·4 (5·0), 101·7 (4·0), and 98·7 (6·9), respectively. The difference in the mean DQ in group A compared with groups B, C, and D was significant ($p<0{\cdot}01$, Mann-Witney U test).

PVL lesions: sequence and extent. Thirteen infants were found to have PVL changes in the frontal areas, six in the frontal-parietal areas, and five in the frontal-parietal-occipital areas. The sequence of PVL changes and the extent of the lesion related to size and site of the ultrasonographic appearances are shown in Table 2. Seventeen infants were noted to have the echogenic stage of PVL within the first week of life and seven presented only with the late stage, with small cystic cavitations of 1–2 mm, close to the external angles of the lateral ventricles.

The most common sequence of PVL changes was increased echogenicity that resolved into cystic formations (11 cases). In five infants sequential scanning revealed a persistent increased echogenicity lasting at least two weeks. This was located in the frontal areas in three infants, in the frontal-parietal areas in one, and in the frontal-parietal-occipital areas in one. Cystic changes were not identified in spite of serial ultra-sonography in these patients. The extent of the lesion was related to the

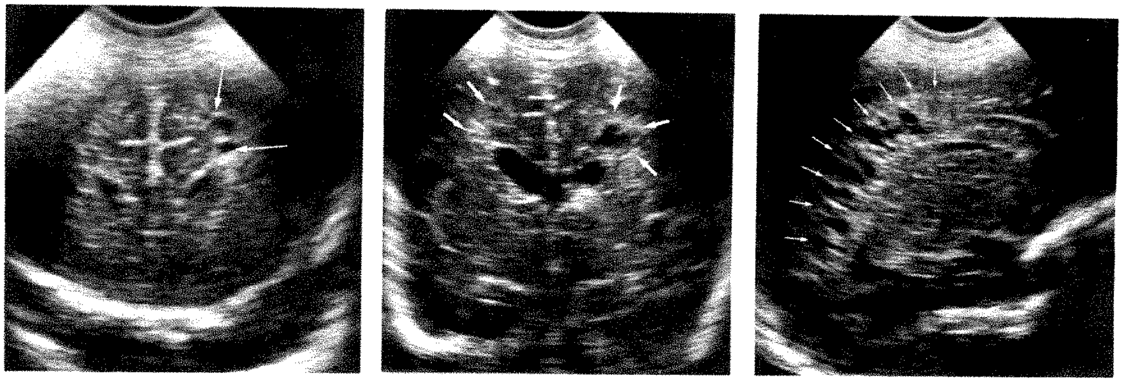

Fig. 3 *Multiple cystic formations in the frontal (coronal scan (left), parietal (coronal scan) (middle), and occipital areas (parasagittal scan) (right).*

Table 2 *Periventricular leucomalacia: localisation, sequence, and extent*

Type of leucomalacia	*Sequence of PVL changes*		*Extent of lesion*	
	Early stage (1st week)	*Late stage (2nd–12th week)*	*Size (echogenic or cystic area)*	*Site*
Frontal (n=13)	5 echogenic	Cystic	Cysts of 1–2 mm	Anteriorly to or around the frontal horns
	3 echogenic	Echogenic	Small focal increased echogenicity	
	5 —	Cystic	Cysts 1–2 mm	
Frontal-parietal (n=6)	1 echogenic	Echogenic	Large triangular increased echogenicity	Both frontal-parietal areas
	2 echogenic	Cystic	Multiple small cysts (1–2 mm)	Around external angles of lateral ventricles in frontal and parietal areas
	1 echogenic	Cystic	1 large right cyst	Right parietal area
	2 —	Cystic	Small cysts of 1–2 mm	Both frontal-parietal areas
Frontal-parietal-occipital (n=5)	1 echogenic	Cystic	Cysts of 2–5 mm	Both frontal-parietal-occipital areas
	2 echogenic	Cystic	Large cysts of > 1 cm	Both frontal-parietal-occipital areas
	1 echogenic	Echogenic	Extensive increased echogenicity	Both frontal-parietal-occipital areas
	1 echogenic	—	Pronounced increased echogenicity	Both frontal-parietal-occipital areas

PVL=Periventricular leucomalacia.

site of PVL. Frontal lesions were all focal or of small size. Most of the infants with frontal-parietal and frontal-parietal-occipital damage had large lesions.

Neurodevelopmental outcome in relation to PVL lesions. The distribution of the DQ on the Griffiths scale with regard to the site of PVL is shown in Figure 4. All children with frontal leucomalacia were normal and had a DQ above 80. Major handicap was found in three of the six children with frontal-parietal leucomalacia. The three normal children had only small cystic formations 1–2 mm in diameter clustered around the external angles of the lateral ventricles. Infants with extensive lesions involving the frontal-parietal-occipital areas had a poor prognosis, and most had a DQ below 80.

Major handicaps and PVL lesions. Patients with PVL lesions and major handicaps are described in Table 3. All but two infants had PVH in association with PVL lesions. Ventricular dilatation was also common and two infants required ventriculocardiac shunting. PVL was detected within the first days of life in its echogenic stage in each infant. The echogenic areas resolved into cystic cavitations of various size in all but two infants (cases 1 and 6). Case 8 developed signs of cerebral atrophy (enlarged extracerebral spaces and prominent interhemispheric and sylvian fissures) after a very rapidly progressive hydrocephalus, which might suggest diffuse hypoxic-ischaemic parenchymal damage. The cysts were large (>1 cm in diameter) in cases 2, 5, and 7. Multiple small cysts 1–2 mm in diameter surrounding the external angles all along the ventricular system were found in two patients (cases 3 and 4). Most of the children had extensive involvement of the frontal-parietal-occipital areas (cases 4–8).

Six children with parietal lesions developed moderate to severe motor dysfunction: two had a spastic diplegia, one hemiplegia, and three spastic quadri-

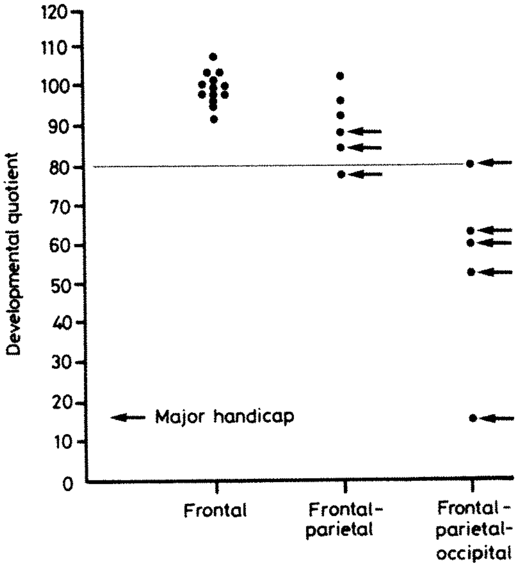

Fig. 4 *Development quotients on the Griffiths scale according to the distribution of periventricular leucomalacia.*

Table 3 *Patients with major handicaps and PVL lesions*

Case No	*Gestational age (weeks)*	*Ultrasound*		*PVL lesions*			*Outcome*		
		PVH grade	*Ventricular dilatation*	*Early stage*	*Late stage*	*Site*	*Cerebral palsy*	*Other handicaps*	*Developmental quotient (Griffiths scale)*
1	28	—	Transient	Echogenic	Echogenic	Frontal-parietal	Moderate spastic diplegia	—	93
2	33	II	Arrested	Echogenic	Large right cyst	Frontal-parietal	Left hemiplegia	Squint	85
3	29	II	—	Echogenic	Multiple small cysts	Frontal-parietal	—	Developmental delay	78
4	28	II	Arrested	Echogenic	Multiple small cysts	Frontal-parietal-occipital	—	Mental retardation, severe visual impairment	60
5	34	I	Transient	Echogenic	Large cysts	Frontal-parietal-occipital	Severe spastic diplegia	Mental retardation left hemianopsia	53
6	32	—	Arrested	Echogenic	Echogenic	Frontal-parietal-occipital	Severe spastic quadriplegia	Severe visual impairment	63
7	30	III	Shunted	Echogenic	Large cysts	Frontal-parietal-occipital	Severe spastic quadriplegia	Mental retardation, severe visual impairment seizures	15
8	28	II	Shunted	Echogenic	Cerebral atrophy	Frontal-parietal-occipital	Moderate spastic quadriplegia	Squint, myopia	80

PVH=Periventricular-intraventricular haemorrhage; PVL=periventricular haemorrhage.

plegia. Only two children with minor parietal involvement (small cysts) did not have cerebral palsy (cases 3 and 4). The five children with extensive lesions in the frontal-parietal-occipital areas presented with multiple handicaps. Severe visual impairment was found in four infants with occipital lesions: three had uncoordinated eye movements, nystagmus, reduced visual acuity, or no apparent vision and one had poor visual activity and a left hemianopsia related to right occipital PVL. Hearing was normal in all. Development was delayed (DQ <80) in most of them.

Discussion

The present study indicated that major neurodevelopmental sequelae were closely related to the presence of PVL. Our data also confirmed previous reports describing a good prognosis for uncomplicated, small, or isolated periventricular-intraventricular haemorrhage.[8 18–22] The interpretation and importance of the ultrasound scan findings, and more particularly increased periventricular echogenicity, has been disputed.[11 23 24] The diagnosis of PVL by ultrasonography and assessment of the prognosis of this lesion requires (1) systematic and sequential scanning in the neonatal period to allow precise detection and description of the lesions, (2) the use of mechanical sector scanner with high frequency transducer to visualise both the periventricular white matter and parenchyma and to identify small lesions, and (3) a follow up programme of all scanned infants whatever the ultrasonographic diagnosis to assess and compare prospectively their neurodevelopmental outcome.

We have previously reported in an autopsy correlation study that the early changes of PVL—that is, increased echogenicity corresponding on microscopy with acute coagulation necrosis[5]—evolved into two different patterns.[4] The most common change was cystic degeneration with well circumscribed echofree areas. The second change appeared as a persistent increased echogenicity (Fig. 5) lasting two to four weeks and was probably caused by gliosis with microcalcifications and small cysts less than 2 mm in diameter[4 25] not identified by our scanning equipment. These observations strongly suggest that PVL and haemorrhage originating from the germinal layer are two distinct entities because of their respective topography and microscopic changes. Germinal layer haemorrhage may extend into the ventricular system and parenchyma. In our experience, however, 'parenchymal haemorrhage' is rare.

The extent of the damage was related to the size of the hyperechogenic area and the size, number,

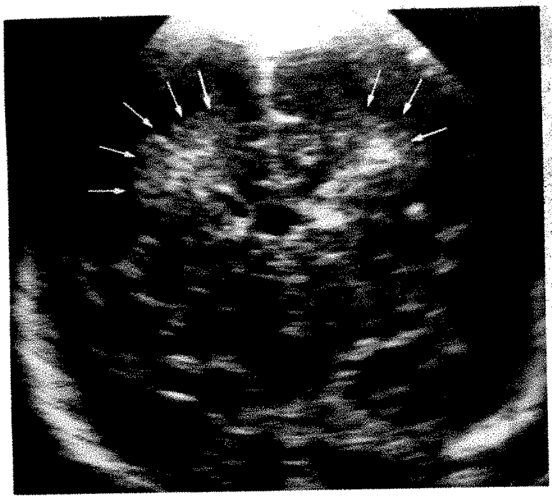

Fig. 5 *Coronal scan at 2 weeks of age, showing a persistent increased echogenicity in the parietal areas.*

and site of the cysts. As already described in neuropathological reports[25 26] PVL varied considerably in frequency and site. The preferential distribution in our study was in the frontal areas, anteriorly to the frontal horns. The periventricular white matter of the parietal regions, at the level of the foramen of Monro in the centrum semiovale, was also often affected. Involvement of the occipital radiations, at the trigone of the lateral ventricles, was always associated with extensive damage located in the frontal and parietal areas. Lesions were most often bilateral and multiple. These results support the idea that hypoxic-ischaemic injuries occur in the 'watershed' areas of the central and cortical vascular supplies and in the boundary zones between the main cerebral arteries.[27–29]

Major neurodevelopmental handicaps were strongly associated with the presence of PVL. A clear relation could be established between the type and severity of the dysfunction and the site and extent of the cerebral lesions. Parietal involvement led to motor dysfunction. The more extensive the damage the more severe the cerebral palsy. A severe visual impairment was found in most infants with occipital lesions. Infants with frontal PVL or small focal changes of PVL, however, had a good prognosis. None of them had a major handicap and at 18 months their development was considered normal.

Surprisingly, two children who were sequentially scanned had only the persistent hyperechogenic appearance of PVL with no cystic cavitation, yet they presented with severe sequelae. Leech showed a broad variety of microscopic alterations of PVL, which suggested a gradient of insult.[30] Our findings supported this hypothesis and seemed to indicate that the persistent increased echogenicity is likely to reflect permanent microscopic changes resulting in neurologic deficit. Furthermore, small cysts 1–2 mm in diameter, if multiple, might also represent a marker of a more diffuse parenchymal ischaemia, causing a severe developmental delay or a mental retardation (cases 3 and 4).

We conclude that serial brain ultrasonography in the newborn has an important role in the prediction of later neurodevelopmental outcome among preterm infants. It is as important to describe the persistent echogenic appearance of PVL as the cyst formation because major handicaps in our study could be ascribed to both these lesions. A relation between site and extent of the lesions and type and severity of the handicap was shown. Further follow up studies are needed to assess fine psychometric abilities and cerebral function in children with focal or frontal PVL who were apparently 'normal' at 18 months.

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Non-convulsive status epilepticus

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SUMMARY Status epilepticus can complicate any type of seizure activity. A group of 13 children with non-convulsive status has been studied. Five presented with chronic fluctuating neurological features, while eight had intermittent episodes of their atypical status, although each of these lasted for several days. The clinical features, treatment, and outcome for these groups of children are described. Most of the children in both groups are mentally retarded after regressing at the time of their status epilepticus. The recognition and aggressive treatment of atypical status is important in reducing the risk of subsequent mental handicap.

Status epilepticus is one of the common medical emergencies of childhood. The term is usually used to describe repeated tonic-clonic seizures with intervening loss of consciousness. In this form recognition is easy and without prompt and vigorous treatment considerable morbidity and mortality may ensue.[1]

Status epilepticus can complicate any type of seizure activity. The familiar 'convulsive' status is but one manifestation of a range of illness. Other more insidious presentations, which are by no means rare in childhood, have been recognised. This paper documents and gives case histories of less common forms of status epilepticus with a view to highlighting aspects of presentation, treatment, and prognosis.

Patients and methods

The children studied were those admitted to the regional paediatric neurology unit at our hospital between 1971 and 1984 with status epilepticus other than tonic-clonic status. All children had repetitive or fluctuating neurological symptoms coinciding with continuous spikes or slow waves, or both, on the electroencephalogram (EEG). Seizures were classified according to the proposal for revised clinical and electroencephalographic classification of epileptic seizures.[2] In some children the neurological symptoms lasted from weeks to several months. These children had extensive metabolic, neurophysiological, and, where appropriate, neuroradiological investigations performed to exclude other possible causes of their symptoms.

Thirteen children (six boys and seven girls) were studied. Twelve children were known to have epilepsy and one had never suffered classical seizures. The children were divided into two groups by mode of presentation, periodicity of symptoms, and difficulty of seizure control.

Group 1. Chronic, fluctuating neurological symptoms with electrical status (Table 1).

Clinical features

These children presented insidiously with fluctuating symptoms and very prolonged episodes of status, lasting from one to 24 months. Two children presented with intermittent ataxia but minimal impairment of consciousness. One of these had never suffered classical seizures. Two further children had intermittent receptive and expressive dysphasia, in one case associated with a prolonged fugue state. The fifth child showed fluctuating unresponsiveness and developmental regression. In spite of relevant and extensive neurological investigations[3] no underlying causes for the children's symptoms were ascertained. Clinical relapses were always associated with electrical status.

Table 1 *Characteristics and epilepsy type in the two groups: Group 1, children with chronic, fluctuating symptoms; Group 2, children with episodic, acute status*

	Group 1 *(n=5)*		*Group 2* *(n=8)*	
Male:female	1:4		4:4	
Age range (median)	10 months–10 years (14 months)		7 months–11 years (7 years)	
Seizure type	Atypical absences:	3	Myoclonic:	5
	Complex partial:	1	Complex partial:	2
	No previous fits:	1	Unilateral:	1

Treatment

Table 2(a) gives the response to treatment with drugs. Because of the insidious symptoms no child was given intravenous anticonvulsants at presentation. In the three children given adrenocorticotrophic hormone EEG improvement accompanied clinical remission, but relapse occurred on withdrawal and repeated courses were required. Treatment with sodium valproate in one child with intermittent ataxia resulted in sustained clinical and EEG improvement. In a girl with complex partial status treatment with clonazepam was effective after carbamazepine, phenytoin, and phenobarbitone had been unsuccessful.

Outcome

Seizures were well controlled in all cases (<1 per month) and in two children anticonvulsants were eventually stopped without ill effect. The outlook for intellectual development, however, was not so favourable. Mental regression occurred in four of the five children during the period of their electrical status, and in each case deterioration halted but did not reverse when the tendency to status abated.

Group 2. Acute, recurrent episodes of status with poorly controlled epilepsy (Table 1).

Clinical features

Among these children episodes of status were characterised by increasing frequency of their usual seizure type, most commonly myoclonic jerks, atonic attacks, and automatisms. There was variable impairment of responsiveness, but in no case was there loss of consciousness. Drooling, ataxia, disorientation, and aggressive behaviour were often noted. The duration of status ranged from three days to four weeks. In several children there was a history of deteriorating seizure control for weeks before presentation. In only one child was a potential precipitating factor (reduction in phenobarbitone dosage) identified. Again investigations failed to identify underlying diseases.

Treatment

Table 2(b) indicates the poor response to intravenous diazepam, particularly among children with myoclonic status. Altogether, diazepam was only effective in two cases. Other drugs, notably clonazepam and chlormethiazole, were usually required. Stopping of intravenous treatment resulted in relapse in four cases of myoclonic status.

Outcome

All of these children had poorly controlled epilepsy (>1 seizure per month). At the time of writing four children continued to suffer daily seizures, and three of these have suffered further episodes of myoclonic status. The outlook for intellectual development was poor. Regression in association with their status epilepticus occurred in four cases. Extensive investigation revealed no cause other than recurrent status for this regression. Four children had computed tomograms taken two months after the episodes of status. These yielded normal results in two, but the other two had evidence of cerebral atrophy. Again control of status did not result in intellectual improvement in any case but merely halted further deterioration.

Table 2 *Response to treatment with drugs in the two groups*

Case no	*Seizure type*	*Treatment with drugs*	
		Ineffective	*Effective*
(a) Group 1, children with chronic, fluctuating status			
1	No seizures		Sodium valproate
2	Complex partial	Carbamazepine	Clonazepam
3	Atypical absences	Sodium valproate; clonazepam	ACTH
4	Atypical absences		ACTH
5	Atypical absences		ACTH
(b) Group 2, children with episodic, acute status			
6	Myoclonic	Diazepam	Clonazepam
7	Myoclonic	Diazepam	Chlormethiazole
8	Myoclonic	Diazepam	Chlormethiazole
9	Myoclonic	Diazepam; chlormethiazole	Clobazam
10	Myoclonic		Diazepam
11	Complex partial	Diazepam; phenytoin	*
12	Complex partial	Clonazepam	Diazepam
13	Unilateral	Diazepam	Clonazepam

*Spontaneous resolution.
ACTH=Adrenocorticotrophic hormone.

Illustrative case histories

Case 1. A 3 year old girl had a six month history of fluctuating gait disturbance. She had suffered an episode of ataxia one year previously. There were no perinatal or developmental problems nor a history of seizures. On examination she was hypotonic with an ataxic, broadbased gait. Metabolic and virologic studies yielded negative results and a computed tomogram was normal. The EEG showed continuous, generalised, high amplitude spike and slow wave discharges. She was treated with sodium valproate. The ataxia improved during the next few months, coinciding with EEG improvement. Intellectual development was normal.

Case 2. This 10 year old girl had a one year history of deteriorating school performance and personality change. She had become progressively more withdrawn and had prolonged episodes of vacant staring. There was variable attention deficit and she constantly answered 'Pardon?' when asked questions. Writing ability deteriorated and there was expressive dysphasia with persistent word confusion. She had suffered tonic-clonic seizures since the age of 18 months, which were well controlled by sodium valproate. On examination she was in a fugue state but was cooperative. Psychometric testing showed poor auditory memory and verbal coding and a reading age of 8·1 years. The EEG showed continuous high amplitude spike and slow wave activity with left temporal preponderance. Carbamazepine was introduced, but the fugue state persisted virtually unabated for a year with persistent expressive dysphasia and EEG evidence of status. At 11 years her reading age was 7 years. After introduction of clonazepam there was a gradual improvement with resolution of the personality change and improved word finding. At 13 years the reading age was 11·4 years and speech was fluent. Full scale intelligence quotient (Wechsler intelligence scale for children) was 77, the EEG was normal, and clonazepam was successfully withdrawn.

Case 8. This boy presented at 4 years with a three day history of myoclonic and atonic attacks and intervening lethargy, ataxia, and aggressive behaviour. Developmental progress was normal until 3 years when he suffered an episode of tonic-clonic status epilepticus during an upper respiratory tract infection. He subsequently developed myoclonic-atonic epilepsy, which was poorly controlled by anticonvulsants. On examination he was lethargic, ataxic, and dysarthric. Frequent myoclonic jerks and atonic attacks were observed. The EEG showed continuous, generalised, high amplitude, irregular polyspike and slow wave discharges. Intravenous diazepam produced some EEG improvement but no clinical change. Infusion of chlormethiazole ended the episode but relapse occurred on withdrawal and intravenous clonazepam was subsequently effective. The total duration of status was four weeks. Two further episodes occurred and were terminated by clonazepam. At the time of writing he was continuing to have daily seizures while receiving a combination of phenytoin and nitrazepam and was mildly mentally retarded. A computed tomogram taken two months after the initial episode of status showed mild cortical atrophy.

Discussion

In their usual forms myoclonic, absence, partial, and unilateral status share many similarities with tonic-clonic status. The epilepsy of affected children is typically resistant to treatment and deteriorating seizure control culminates in continuous seizures of the type usually suffered by the child. In contrast to tonic-clonic status impairment of consciousness is marginal and the ictal state is associated with dulled responses, automatisms, drooling, ataxia, and behaviour disturbance. Episodes are often prolonged and resistant to treatment with intravenous diazepam.

Of perhaps greater interest is a group of children who present more insidiously with chronic neurological symptoms, such as ataxia, dysphasia, and unresponsiveness. Symptoms, while fluctuating, are not clearly episodic and may persist with varying degrees of severity for years. Alterations in responsiveness are subtle and impairment of consciousness minimal. Most of these children have a past history of epilepsy (complex partial or atypical absences), but this has usually been well controlled and remission is common. It is not surprising, therefore, that the inherent 'epileptic' nature of the symptoms may not be initially recognised. Given the periodicity of the symptoms, the EEG evidence of status, the exclusion of other potential causes, and the response (albeit temporary) to anticonvulsants, however, there is no doubt that these children are in status epilepticus and should be treated accordingly. An index of suspicion is crucial as diagnosis (by EEG) is straightforward.

Brett first drew attention to ataxia as a symptom of minor epileptic status.[4] He considered that this 'pseudoataxia' was due to the intrusion of repeated myoclonic jerks. Ataxia may result from disruption of cortical connections as well as reflecting cerebellar or peripheral nerve disease. It may, therefore, be a symptom of diffuse cortical disease. The two children presented here with intermittent ataxia showed several of the features outlined by Brett, notably prolonged fluctuations in symptoms, similar EEG changes, and in one case temporary improvement with adrenocorticotrophic hormone but ultimate dementia.

Dysphasia is a well documented manifestation of non-convulsive status, particularly complex partial status.[5-8] De Pasquet *et al* reported dysphasia lasting three weeks in a 17 year old boy with complex partial status.[5] Kellerman described recurrent aphasia and personality disorder in a 6 year old boy with sleep induced electrical status.[7] In both cases language difficulty persisted after status had resolved. Dysphasia in the two cases reported here was much more prolonged (lasting one and two years, respectively) and was less clearly episodic. Although there was gradual resolution in both cases, there were residual difficulties with language comprehension and mild mental retardation.

The most worrying feature of the children presented in this series is the poor prognosis for intellectual function. Ten children were ultimately retarded, whereas only four were before the episodes of status. Investigations failed to elucidate other possible causes of regression. The implication is that 'minor' epileptic status, no less than generalised tonic-clonic status, can cause brain damage. Several authors provide evidence in support of this. Brett reported that 10 of 22 children with minor epileptic status showed intellectual regression.[4] Doose and Volzke, in a review of 117 children with myoclonic-astatic epilepsy, found a close correlation between status and dementia.[9] Fifty two per cent of children who had suffered status were severely retarded compared with 24% of those who had not. Ohtahara *et al* reported that eight of 25 children with non-convulsive status regressed.[10]

There is no evidence that successful treatment can improve intellectual function. The aim is to prevent further deterioration, and treatment, therefore, should be just as prompt and vigorous as for convulsive status. Given the potentially prolonged nature of episodes and the poor response to diazepam, the use of other drugs, such as clonazepam or chlormethiazole, should be considered early in the course of presentation. In young children with chronic symptoms and electrical status adrenocorticotrophic hormone may be effective. As the effect is often transient perhaps treatment should be continued for prolonged periods.

The nomenclature of status epilepticus has been confusing.[10-12] Terms such as 'non-convulsive' and 'minor motor' status have been used to embrace types of status other than generalised tonic-clonic status and may imply that these types are less severe. Gastaut has stated that there are 'as many types of status epilepticus as there are types of epileptic seizure'.[13] Acknowledgement of this fact facilitates earlier recognition of less common types of status, emphasises the potential for brain damage, and provides a rational basis for aggressive treatment.

We are grateful to our colleague, Dr J R Roberts, for permission to report on children under his care.

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Non-convulsive status epilepticus resistant to benzodiazepines

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SUMMARY We describe the failure of an intravenous benzodiazepine to control non-convulsive status epilepticus occurring in six patients with the Lennox-Gastaut syndrome. In one patient the benzodiazepine induced a paradoxical response with clinical and electroencephalographic seizures.

Non-convulsive status epilepticus is a rare but serious complication of seizure disorders in childhood, particularly in the age dependent epileptic encephalopathies, such as the Lennox-Gastaut syndrome.[1] The effects of non-convulsive status on cerebral metabolism are uncertain. In children with intractable seizure disorders, however, the incidence and degree of subsequent mental retardation is greater in those who have had one or more episode of non-convulsive status compared with those who have had no episodes.[1 2] In addition, during these episodes, the children are very slow to react to any stimuli, are unable to concentrate, have no ability to learn, become disorientated and confused, and often lose speech. Episodes of non-convulsive status may last from a few hours up to several months.[3] For these reasons such episodes are regarded by many as a paediatric emergency requiring aggressive treatment.

While it is recognised that non-convulsive status may be drug resistant, in general intravenous benzodiazepines have been considered to be the drugs of choice for this complication.[2–4] Gastaut has gone as far as to say that all cases of absence status respond within a few minutes to intravenous benzodiazepines.[5]

We report here our experience with seven patients presenting in non-convulsive status treated with benzodiazepines.

Patients and methods

The patients reported here formed part of a group of 40 patients with intractable seizure disorders in whom testing of benzodiazepine sensitivity has been carried out. Nine out of the forty (23%) had an electroclinical diagnosis of the Lennox-Gastaut syndrome, and seven of these nine presented with at least one episode of non-convulsive status. These seven patients had testing of benzodiazepine sensitivity performed during the acute episodes of status and form the subject of this paper.

Details of the seven patients are shown in the Table. All patients were attending the paediatric epilepsy service at the Royal Hospital for Sick Children, Edinburgh. There were four boys and three girls. The mean age of presentation was 7 years (range 3–13 years). The aetiology in all cases was unknown, but in one patient it was presumed to be prenatal in origin as he showed dysmorphic features with microcephaly. The usual seizure type in most patients comprised drop attacks, complex absences, myoclonic jerks, and tonic seizures. All patients had presented with increased frequency in their usual seizures, followed by onset of unresponsiveness, drooling, and prolonged absences, in some cases associated with loss of speech and ataxia.

In all the patients the electroencephalogram (EEG) showed continuous or almost continuous slow spike or polyspike and wave of varying degrees of symmetry and synchrony. The duration of status as determined by history ranged from two days to five weeks (mean 10 days).

All patients were given intravenous benzodiazepines during continuous EEG monitoring. Five patients were given diazepam in a dose of 0·2–0·3 mg/kg, one was given clonazepam in a dose of 0·02 mg/kg, and one was given both clonazepam and diazepam.

Results

Examples of the EEG response to intravenous benzodiazepines are shown in the Figure. Only one

Table *Clinical features and results of testing in the seven cases*

	Case No						
	1	*2*	*3*	*4*	*5*	*6*	*7*
Sex	M	M	F	F	F	M	M
Age (years)	13	5	7	8	7	7	5
Past history	Febrile convulsions	Developmental delay microcephaly, hyperactive	Prolonged and recurrent febrile convulsions	Recurrent febrile convulsions, afebrile convulsions, hyperactive	Tonic/clonic seizure aged 5	Dysmorphic, microcephaly, developmental delay, onset absences aged 2½	Onset infantile spasms at 6 months, mental retardation
Diagnosis	Lennox-Gastaut	Lennox-Gastuat	Lennox-Gastaut	Lennox-Gastaut	Lennox-Gastaut	Lennox-Gastaut	Lennox-Gastaut
Aetiology	Unknown	Unknown	Unknown	Unknown	Unknown	Presumed prenatal	Unknown
Usual seizure type	Drop attacks, tonic/clonic, myoclonus	Drop attacks, absences	Drop attacks, absences, tonic/clonic	Drop attacks, tonic/clonic, absences, myoclonic	Drop attacks, absences, erratic myoclonus, tonic seizures	Adversive seizures, drop attacks, absences, tonic/clonic	Drop attacks, absences, myoclonic tonic/clonic
Drugs at time of presentation	None	None	Carbamazepine, clonazepam	Carbamazepine, valproate	Carbamazepine, primidone, acetazolamide, ethosuximide	Valproate	Valproate, carbamazepine
Previous use of benzodiazepines	Yes	No	Yes	Yes	Yes	No	Yes
Clinical features	Drowsy, frequent brief twitches of mouth and hands, drooling	Ataxic, frequent brief twitches of hands, 'dazed appearance'	Drooling, unresponsive, unable 'to walk', brief myoclonic jerks, increase in tonic seizures	Frequent prolonged absences, drooling tonic/clonic seizures, myoclonic jerks	Increased frequency seizures, drooling, ataxic, unresponsive	Prolonged unresponsiveness, frequent atonic seizures, erratic myoclonus	Drowsy, ataxic, unresponsive, frequent drop attacks, increase in myoclonous
Estimated duration of status	Two days	Uncertain, probably several weeks	Three days	Several weeks	At least four days	Two weeks	Two weeks
Electroencephalogram appearance	Continuous, high amplitude, generalised slow spike and wave	Continuous, slow spike and wave at 2 Hz, right more than left	Continuous, moderate amplitude, irregular slow with runs of spike and slow waves	Almost continuous, generalised slow spike and wave with occasional high amplitude polyspikes	Very frequent generalised spike and wave at 2·5–3·5 Hz	Continuous, high amplitude, asynchronous slow spike and wave at 2 Hz, with occasional suppression	Continuous, high amplitude, slow spike and wave
Response to benzodiazepines	Paroxysmal response, induced tonic seizures	Modification of spike component but no change in background	No change	No change	No change	Increase in episode of suppression but still almost continuous paroxysmal activity	Complete suppression of paroxysmal activity, emergence of more normal background

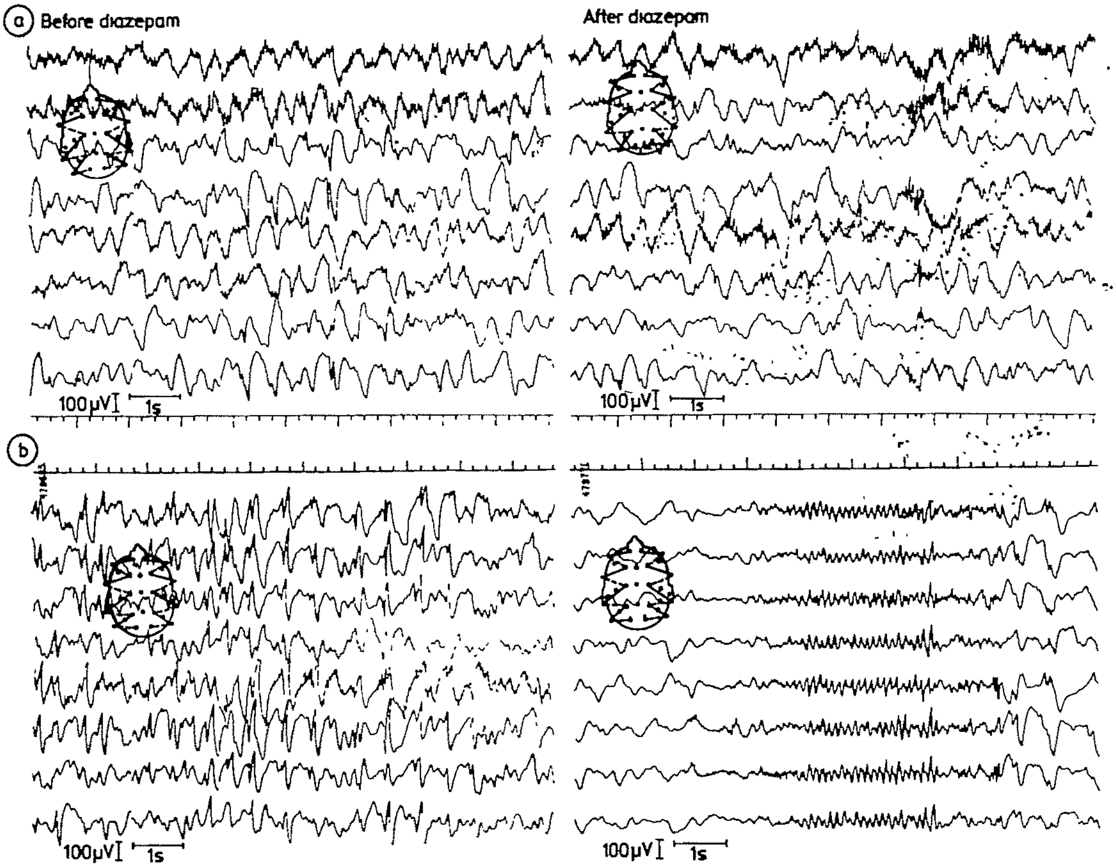

Figure (a) *Example of non-response to administration of diazepam in case 3; (b) Paradoxical response occurring in case 1 associated with tonic seizure.*

patient showed a positive response with complete abolition of paroxysms and improvement in clinical state after treatment with benzodiazepines. One patient (case 6) showed a change in his EEG with an increase in the number of episodes of suppression but still with virtually continuous paroxysmal spike and wave activity and no associated clinical improvement One patient showed some modification of the spike component but continued with high amplitude slow wave background activity and no clinical change. One patient (case 1) had a paradoxical response with the onset 10 minutes after administration of benzodiazepines of paroxysms of rhythmic spikes at 10 per second followed by spike and wave. On each occasion these paroxysms were associated with a tonic seizure. Three patients showed no change in their EEG or clinical state

Discussion

These results suggest that the benzodiazepines may not be the most effective treatment for non-convulsive status. It is well known, however, that the effects of the benzodiazepines are unpredictable and that patients' sensitivity to the drugs may change with time, depending on such variables as current anticonvulsive treatment and seizure control.

Lagenstein reported a 57% response rate to intravenous benzodiazepines in 56 patients with a diagnosis of petit mal status. They also reported, however, a high relapse rate.[6] In contrast, Tassinari found that only 15% of children with non-convulsive status associated with the Lennox-Gastaut syndrome showed EEG or clinical response to intravenous benzodiazepines.[7]

Benzodiazepines act by enhancing γ-aminobutyric acid (GABA) mediated inhibition in the central nervous system by their action on the GABA-benzodiazepine/chloride ionophore complex. There are at least two pharmacologically distinct benzodiazepine receptors, and type 2 probably consists of several subunits. A recent hypothesis suggests that each benzodiazepine receptor has four different binding sites for the benzodiazepines and each of these sites can exist in three different conformations. It is thus theoretically possible for the benzodiazepines to increase, decrease, or have no effect on gabinergic transmission.[8]

In addition, other anticonvulsants are known to interact directly at the benzodiazepine receptor or to have other effects on GABA-mediated inhibition. As well as the conformational and interactional changes that may occur in benzodiazepine receptors, it is also known that changes in receptor numbers may occur with chronic treatment, and thus both down regulation and up regulation of receptors have been described.[9]

Five of the seven patients in this group had previously been on oral treatment with benzodiazepines and thus these mechanisms may explain their subsequent lack of response. Two of the patients, however, had no previous exposure to them and clearly down regulation of receptors could not explain the lack of response in these patients. It does seem, however, that the chronicity of the seizure disorder, together with the need for many different anticonvulsants taken over long periods, seem to make negative or paradoxical responses more likely.

The benzodiazepines are the most effective treatment for convulsive status epilepticus available and from this small series we would not suggest that they should be avoided in the treatment of non-convulsive status. These results illustrate, however, that many patients with non-convulsive status will not respond to them in the acute stage. We would emphasise the importance of continuous EEG monitoring during the treatment of these patients to assess the effects and watch for unusual or paradoxical responses that are more common in this group of patients. If diazepam has failed we would suggest a trial of clonazepam, although in our experience we have not seen anyone in non-convulsive status who has responded to clonazepam that did not respond to diazepam. These states are often very drug resistant, and many different therapeutic manoeuvres have been tried. It has been suggested that infusion of chlormethiazole may enable benzodiazepine sensitivity to return, but this has not been our experience.

In patients who have become resistant to benzodiazepines after a previous response a drug holiday of several weeks may allow sensitivity to return This approach would only have been applicable, however, to one of our patients in this study, as six of the seven were not on benzodiazepines at the time of testing. Clobazam has been suggested to be superior to the other benzodiazepines for chronic oral treatment. Our clinical impression is that, while it does seem more effective in other types of intractable seizure disorders, it has not proved to be an advance in patients with the Lennox-Gastaut syndrome.

If benzodiazepines have failed to control non-convulsive status we would suggest immediate treatment with either regular paraldehyde, infusion of chlormethiazole, or possibly infusion of barbiturates or steroids.

Although there is increasing concern about the possible brain damage caused by recurrent bouts of non-convulsive status, treatment of these states remain frustratingly difficult with the current anticonvulsants at our disposal.

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Screening for polycystic kidney disease: importance of clinical presentation in the newborn

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SUMMARY Fifty per cent of the offspring of adults with the adult (dominant) form of polycystic kidney disease are carriers of the abnormal gene. Clinical symptoms and signs before adolescence are rare, but renal ultrasonography may detect evidence of cyst formation. Twenty two children, all offspring of parents with known adult polycystic kidney disease, have undergone renal ultrasonography. In six cases evidence of disease was detected without clinical manifestations at the ages of 1, 2, 5, 8, 13, and 14 years. There were no renal masses, hypertension, haematuria, or evidence of renal insufficiency.

In four children from three sibships, whose families had no previous history of renal disease, bilateral renal masses were noted to be present at birth. In each case one parent was subsequently found to have adult polycystic kidney disease. At the ages of 1, 4, 6, and 20 years, while renal masses were still palpable, there was no evidence of renal insufficiency or hypertension in the younger children, while the oldest had mild renal failure. An analysis of the reported cases in childhood is suggestive of a bimodal distribution of enlarged kidneys, with a number of cases diagnosed at birth or soon after, followed by an increasing incidence during later childhood. Adult polycystic kidney disease presenting at birth may be qualitatively different from the disease detected by screening programmes of children at risk.

The adult, dominant form of polycystic kidney disease is rarely diagnosed clinically in childhood. As recently as 1976 an eminent nephrologist and expert in childhood hypertension could claim never to have made the diagnosis in childhood and was unable to find a single case with nephromegaly or impaired renal function, or both, in the records of the Los Angeles Children's Hospital or among more than 5000 autopsies [1]

The advent of renal ultrasonography has introduced a safe, non-invasive method for detection of adult polycystic kidney disease, raising issues about whether the offspring of parents with known disease should be routinely screened, at what age it should begin, and how often it should be carried out. Current major paediatric texts express no opinion on this important issue.[2 3]

All potential carriers of the adult disease gene should be offered screening before starting their own families on the basis of informed choice and understanding its nature. As clinical presentation in childhood is rare it remains uncertain how early such screening should begin.

We report our experience with children of parents with adult polycystic kidney disease. Our findings are, we believe, useful in helping paediatricians arrive at a rational approach to this problem We also present data and observations on cases presenting with renal masses in the newborn period.

Patients and methods

The study included two groups of children. The first group comprised subjects referred for screening because one parent was known to have adult polycystic disease of the kidneys. The second group comprised children who were found to have renal masses at birth and one of whose parents was subsequently found to have the disease. These two groups are considered further below

Group 1. Twenty two subjects, from 16 sibships, underwent ultrasonic screening. Ultrasound was carried out at various times until diagnosis had been established Additional investigations included regular blood pressure determinations, urine analysis, and tests on blood creatinine concentrations

Patients with the ultrasound evidence of disease diagnosed on screening all had the characteristic features of renal cysts—that is, a non-reflective area with some enhancement behind it. There was no case of hyperreflective large kidneys resembling the recessive form of polycystic disease usually diagnosed in the neonatal period.

Group 2. This comprised four children followed up for varying periods who had been noted to have renal masses at birth and in whom both the child and one parent were found to have characteristic ultrasound/radiological features

Results

Group 1. The mean age of the children at their most recent screening was 6·25 years, with a range of 1 to 18 years. Six of the 22 cases (27%) have been identified as carriers of the gene at 1, 2, 5, 8, 13, and 14 years, respectively. None of these children had renal masses or other clinical evidence of disease. Two other children had solitary renal cysts of uncertain importance and a further two had had at least one episode of microscopic haematuria at 1 year of age in each case but with normal ultrasonic findings. Whereas under the age of 1 year there were no cases detected, in the age ranges 1–4, 5–8, and 9+ about one third of the children were found to have unequivocal ultrasound evidence of abnormality. The age of first screening and diagnosis or last negative screening are listed in Table 1.

Blood pressure and creatinine concentrations were within the normal range in all screened cases. In no case was systolic or diastolic pressure above the 95th centile of the American task force on blood pressure in childhood at last measurement. Mean systolic blood pressure was 100 mm Hg (median 105 mm Hg), with a range of 80–160 mm Hg, while that for diastolic blood pressure was 62 mm Hg (median 65 mm Hg), with a range of 50–80 mm Hg. Three children had had urinary tract infections. Of these, one had a positive ultrasound scan. Blood urea and creatinine concentrations were within the normal range in all the children

Group 2. Of the children diagnosed by the presence of renal masses at birth, one case had hypertension during the first year of life (maximum blood pressure 160/100), but this settled to normal at 18 months and has remained normal to the age of 6 years. One of the four patients found to have renal masses at birth was in moderate renal failure at 20 years of age (serum creatinine concentration 200 µmol/l). Table 2 summarises the state of these four children.

Table 1 *Details of children screened by ultrasound for adult polycystic kidney disease with an affected parent*

Sibship	*Age (years)*		
	When first screened	*When last screened*	*At positive diagnosis*
1	6	9	—
2a	6	7	—
2b	9	9	—
3	8	8	8
4a	11	13	—
4b	16	18	—
5	<1	2	—†
6	1	1	—†
7a	2	2	—
7b	5	5	—
8	2	3	—
9	<1	2	2*
10a	2	5	—
10b	3	3	—
11	Birth	1	—
12a	13	13	13
12b	14	14	14
13a	Birth	1·5	1·5
13b	Birth	2	—
14	2	2	2
15	7	7	7*
16	5	5	5

*Single cyst only
†Single episode of microscopic haematuria

Table 2 *Details of the four children with adult polycystic kidney disease diagnosed by presence of renal masses at birth*

	Outcome	*Affected parent*	*Renal function*
1a	Well at 6 years	Father	Normal
1b	Well at 1 year	Father	Normal
2	Well at 4 years	Father	Normal
3	Alive at 20 years	Mother	Moderate failure

Discussion

There have been varying reports on the prevalence of clinical features of the adult disease in childhood.[4–6] Most reported cases have been neonates with renal masses. Onset of clinical disease in later infancy and childhood is rarely described.[7–9]

Pathological material either after death or obtained surgically have formed the basis of other studies. Blyth and Ockenden studied 29 cases of renal cystic disease and found six had the adult form.[10] Four were liveborn and two were twin abortuses from a family with a history of cystic kidney disease. There are isolated reports of newborns or neonates who have been found to have cystic kidneys of the dominant type.[11 12] In a similar category are other stillbirths and abortuses with cystic kidneys.[5 10]

Cases may be detected during screening of the offspring of adults with disease or a family history of disease. One such study included 59 children under the age of 12 years among 495 relatives.[13] Sixteen had disease and 10 were considered suspicious, almost reaching the expected prevalence of 50%. There are no details of the ages of the children and whether they had renal masses. Another study of 3379 individuals from 62 families included one infant found to have an abdominal mass at birth.[14] Of 15 subjects screened under 15 years of age, all were negative. This study gives the probability for positive diagnosis between 15 and 19 as 30% (10 out of 33 screened).

In another investigation two cases under 10 years (both negative) and 20 between 11 and 20 years (three positive) were screened.[15] The authors concluded that screening by ultrasound between 10 and 20 years will identify about 30% of the potential cases. Rosenfield *et al* detected renal cysts in 14 of 37 cases between the ages of 18 months and 32 years.[16] Bear *et al* studied 17 kindreds containing a total of 388 persons.[17] Of these, 41 were under 10 years, but only 18 underwent ultrasound examination and two cases were positive Of individuals between 10 and 19, 43 of 69 underwent ultrasound examination and 14 cases were found to be positive. A similar study by Sahney *et al* on 26 cases, of whom 24 were under 25 years, found 17 to be positive on ultrasound examination.[18] Five of the cases were under 15 years and one of these, aged 9 years, was positive Walker *et al* found 11 positive cases out of 22 children aged 5–17 years by a combination of ultrasound, nephrotomography, or pyelography [19]

These series lack the clinical information to allow an opinion to be formed regarding the optimal time to carry out screening in children under 10 years. Our own data indicate that ultrasound examination alone will detect about 70% of the expected cases in a group of children between 1 and 14 years but that with present methods screening otherwise normal babies before 1 year of age is probably not worth while.

Whether an early diagnosis is justified remains an open question. The parents of most of the cases reported here requested screening for their children and expressed a desire to know as soon as possible whether their child was affected or not. The only parent who stated she would rather not have known was the mother of one of the babies found to have renal masses at birth. The knowledge that their child has a 50% chance of being affected seems to be a spur to early identification. In the two cases with single cysts the doubtful importance of the finding was explained with a recommendation for repeat ultrasound in five years.

Ultrasound examination at 1 year and then again at 5 years, followed by five yearly repeats, seems to be a reasonable programme in those families who, understanding the pathogenesis of the disease, still wish to have their children screened at an early age.

It is of interest that while there are more than 20 reported cases presenting with renal enlargement at birth or soon after, there is a relative dearth of reported cases in later infancy and childhood. In the present series, for example, whereas large renal masses were present in the four cases diagnosed at birth, the kidneys were not clinically enlarged in any of the patients diagnosed by ultrasound screening, a finding noted previously.[1] Renal masses are described as the commonest clinical presentation in childhood, but this occurs mainly in the neonatal period. There is no indication in the published reports of the steady increase in numbers of cases with masses that might have been anticipated. The age distribution of reported cases of renal masses seems to be bimodal (Figure). This may be due merely to under reporting, but against this explanation is the fact that among those children who have been detected by screening as positive, enlargement of the kidneys is not a feature

The cases with renal masses in the neonate possibly represent a distinctive group. These

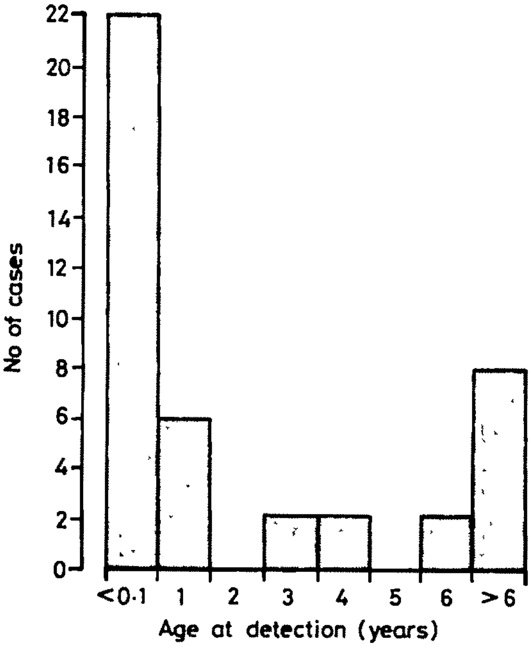

Figure *Age at detection of renal masses of children with adult polycystic kidney disease (reported cases).*

neonatal cases include those where death occurred for various perinatal reasons and cystic disease of the kidneys was detected incidentally at postmortem examination Apart from abortions and stillbirths there are three such cases reported and in none are the kidneys stated to have been clinically enlarged, One was a child detected by prenatal ultrasound examination, presumably as a result of routine screening.[20]

Other neonates suffered early deaths or renal failure related to renal disease. One case with Potter's syndrome and renal masses at birth died of pulmonary oedema due to severe hypertension at 7 months. Another died in renal failure at 3 months, having been noted to have renal masses at 2 weeks. One of the children described by Proesmans *et al* was found to have renal masses and hypertension soon after birth and was in moderate renal failure at 7 years of age.[12] In all these cases the cause of death or renal failure seems to have been due to severe early adult polycystic kidney disease Of 25 infants found to have renal masses at birth, eight had died of perinatal events not related to their kidney disease, while seven were either in renal failure or had died of complications of their renal disease, before the age of 8 years.[21] The neonatal form of the disease (renal masses at birth) seems to have a bad prognosis, yet those cases who did not develop early signs of deterioration seemed to be very well with no evidence of impaired renal function as late as 9 years of age. Even infants with hypertension during early life may have normal renal function in later childhood with apparent disappearance of hypertension (our case 1b).[4] One of our patients is in moderate renal failure at 20 years. The apparent high mortality among newborns found to have renal masses contrasts with the cases diagnosed by screening, who seem to have the same general expectation of survival as adults.

If the cases presenting neonatally do represent a special group several possible explanations might account for this. The gender of the parent with the abnormal gene might determine the occurrence of renal masses in the newborn. This seems to be ruled out by the fact that of the reported cases, in whom the relevant information was available, the affected parent was the father and mother in eight cases, respectively.

The expected frequency of the gene for adult polycystic disease in homozygous form may be estimated as q^2, or one in one million births, where q represents the frequency of the abnormal gene and has a value of 0·001. It might be expected that in homozygous form the gene would have a more severe effect. In no case presenting in the newborn, however, has both parents been shown to have the gene. There seem to be no reported cases of putative homozygous disease.

The same individual might have in heterozygous form both the gene for the adult variety and that for autosomal recessive polycystic disease of the kidney If allelic then both genes would be expected to occur in the same individual with a frequency of 2qr, or six in a million births, where r represents the frequency of the gene for recessive polycystic disease and has a value of 0·003. If not allelic then the frequency would be $2pq \times 2pr$, or 12 in a million births. In either case manifestation might be more 'severe' than in simple heterozygous adult polycystic kidney disease. Either hypothesis would account for the fact that in no fewer than three families there have been siblings reported with neonatal renal masses, an extraordinary coincidence for what is an extremely rare presentation [22] An incidence of 6–12 per million is not inconsistent with the apparent frequency of renal masses due to apparent adult polycystic disease in the newborn.

While ultrasonography remains at present the most effective screening procedure it may well be that the development of gene probes based on the discovery of genetic markers closely linked to adult polycystic disease on chromosome 16 will eventually replace it.[23] This is a technology for the future rather than the immediate present.

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Annual meetings

At York University:
1987 April 7–10
1988 April 12–16
1989 April 11–15

At University of Warwick:
1990 April 3–7
1991 April 16–20
1992 April 7–11
1993 April 19–23 (provisional)
1994 April 11–15 (provisional)

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Scrotal swellings in the under 5s

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SUMMARY Scrotal swelling is a common cause of referral to the paediatric surgical services in Edinburgh, constituting 12% of total admissions. Of these, 2818 (65%) were in boys under the age of 5 years, with a wide variety, including inguinal hernias, hydroceles, testicular torsion, tumours, and some interesting but uncommon conditions. A retrospective study was performed over a 12 year period to assess the incidence, aetiology, mode of presentation, disease, and management of scrotal swellings in boys under 5. Although most of the causes of these swellings were easily elucidated from a history and clinical examination, it was apparent that a high level of suspicion was also necessary to ensure that more serious problems did not go undetected.

This paper studies the incidence, aetiology, disease, mode of presentation, and management of scrotal swellings presenting over a 12 year period (1972–83) in boys under the age of 5 years.

A total of 37 001 patients were admitted to the paediatric surgical wards in Edinburgh (Royal Hospital for Sick Children, Western General Hospital, and Leith Hospital) over this period. Of these, 4341 were due to scrotal swelling, and 2818 of the scrotal swellings were in boys under 5.

The case notes of these patients admitted due to scrotal swelling were examined and assessed by the author and the findings presented.

Findings

Inguinal hernia. A total of 2031 inguinal hernias were seen in boys under 5 during the 12 years These constituted 60% of the total inguinal hernias seen. There was, incidentally, an overall boy:girl ratio of 4:1 in the paediatric age group over this period also. Details of these hernias are given in Table 1.

Hydroceles. A total of 753 hydroceles in the under 5s were operated on during this period (86% of the total hydroceles seen). Of these, 507 (67%) were right sided, 185 (25%) left sided, and 61 (8%) bilateral.

Testicular torsion. Altogether, 25 cases of testicular torsion (or torsion of testicular appendages) were seen within the age group of this study (56% of the total seen). Details of these are given in Table 2.

Tumours. Seven primary intrascrotal tumours were presented in the first five years of life. Ages at presentation ranged from 7 days to 5 years. There were three cases of rhabdomyosarcoma (of epididymis and urachal remnant) and one case each of orchioblastoma, androblastoma, lymphangioma, and benign teratoma. The left to right ratio was 6:1.

All these tumours presented with scrotal swelling. The histories, however, varied from one day (rhabdomyosarcoma) to three months (benign teratoma). The latter case was the only one with a history in excess of two weeks.

Other scrotal swellings. The other scrotal swellings seen were secondary to intra-abdominal problems (blood or chyle after a traumatic vaginal delivery and parenteral feeding fluid after a saphenous vein long line had migrated through a lumbar vein, piercing the peritoneum of the posterior abdominal wall into the peritoneal cavity). There were also a few cases of haematoma and subsequent wound infection after scrotal surgery (orchidopexy or orchidectomy)

Discussion

One in eight admissions to paediatric surgical beds (in Edinburgh) in this study period was due to some type of scrotal swelling. Of these, 65% were in boys under the age of 5. The mode of presentation depended on the underlying disease, but it was not always possible to make a correct diagnosis from history and clinical features alone—for example, acute presentation of boys with testicular neoplasm. By far the most common scrotal swellings were due to a patent processus vaginalis, which constituted 98% of total swellings

Inguinal hernias. It is estimated that 1–3% of children develop an inguinal hernia and that there is a pronounced preponderance of boys (6 1 boy to girl ratio).[1] In this series, however, the boy to girl ratio was much less at 4:1. A total of 60% of the hernias presenting to this unit were in boys under the age of 5.

It can be seen from Table 1 that there was a 3:2 ratio of right sided to left sided hernias, which corresponds to the findings in most other series Our incidence of bilateral hernias, however, was only 8·5%, which is much less than others have reported. Two hundred and fifty one (12%) patients with inguinal hernia subsequently developed a contralateral hernia The incidence of contralateral hernia was much higher in those who originally presented in the neonatal period (27%) than in those who presented later (12%), as others have described.[2] The incidence of irreducible inguinal hernias and their outcome varied with the age of the child at presentation, as follows.

There were 37 inguinal hernias in boy neonates. Of these, 27 (73%) were irreducible at presentation Of these 27 irreducible hernias, 14 reduced spontaneously after analgesia and head down position or gallows traction and/or gentle manipulation/taxis. At surgery in the 13 cases that failed to reduce seven had viable bowel on exploration, but six (22% of the total) contained infarcted small bowel that required resection

There were 72 irreducible hernias in this age group, and of these, 55 reduced on conservative management. The other 17, however, were explored, and two (3% of the total) required bowel resection.

The overall incidence of irreducibility was 5%, and of these, 8% contained ischaemic bowel.

It is thus clear that the early diagnosis and management of irreducible inguinal hernias is vital in all cases but especially in the neonatal period when morbidity and mortality are significantly greater. There were nine recurrent inguinal hernias (0·4%) in this series, which is similar to that found in other series.[3]

Hydroceles. There were 753 congenital hydroceles treated surgically during this period. These were in boys in whom the processus vaginalis had remained patent in excess of 18 months after birth or in whom a tense hydrocele was causing pain and discomfort or difficulty in excluding any underlying disease (testicular torsion or tumour).

Table 1 *Details of inguinal hernias in boys presenting under the age of 5 years*

	Total No of hernias	*Type of hernia*			*Acute presentation (irreducible)*	*No responding to sedation and manipulation*	*No requiring bowel resection*	*Recurrences*	*Contralateral hernia*
		Right sided	*Left sided*	*Bilateral*					
Age at presentation									
Neonatal	37	30	4	3	27	21	6	0	10
4 weeks to 5 years	1994	1067	757	170	72	70	2	9	241
Total	2031	1097	761	173	99	91	8	9	251

Table 2 *Details of testicular torsions in boys presenting under the age of 5 years*

	Total No of cases	*Type of torsion*				*Orchidectomy*
		Right sided	*Left sided*	*Testicular*	*Testicular/ epididymal appendage*	
Age at presentation						
Neonatal	6	6	0	6	0	4
4 weeks to 5 years	19	5	14	15	4	3
Total	25	11	14	21	4	7

Torsion. It can be seen from Table 2 that there were 25 cases of torsion of the testis or its appendages. Again the findings differed depending on age at presentation.

Six cases presented in the neonatal period, all with right sided testicular torsion. Of these, five were extravaginal (common) and one intravaginal (rare).

At operation four testes were gangrenous and removed, but the vascularity of two testes, which were described as 'dusky', improved on resolution of the torsion and were salvaged.

There were 19 cases who presented outside the neonatal period, of whom 14 had left sided and five right sided lesions. Of these, there were 15 testicular torsions and four cases of torsion of the appendices (four hydatids of Morgagni and one organ of Giraldés). Of the 15 testicular torsions, three were irreversibly ischaemic and therefore removed.

The diagnosis and early management of testicular torsion is essential if the testis is to be saved. This is especially so in the neonatal period when the chances of testicular salvage are very poor.[4]

Neoplasms. The incidence of testicular neoplasms in the paediatric age group has been estimated to be roughly 2 per 100 000, with most occurring within the first two years of life.

In this series 0·25% of scrotal swellings were due to an intrascrotal tumour. The age range at presentation was 7 days to 5 years. Four of our cases (57%) were over the age of 2 years There was a pronounced preponderance of left sided tumours (6:1). Most intrascrotal tumours present as a slowly enlarging lesion, but in this series only one case had a history in excess of two weeks. There were two cases (rhabdomyosarcoma) with a very short history of less than two days, which presented as emergencies with acute scrotal pain and swelling where the final diagnosis was made at immediate exploration to exclude testicular torsion or intrascrotal trauma. Thus the history and clinical features did not suggest neoplasia, and only a very high level of suspicion will prevent these lesions being missed at presentation. All tumours were treated by orchidectomy (after first ligating the spermatic cord at the level of the deep inguinal ring). Three tumours were treated with adjuvant chemotherapy, and one required radiotherapy. There was one death six months after diagnosis (a case of rhabdomyosarcoma or urachal remnant who presented with a 24 hour history of scrotal swelling and widely disseminated disease).

Other scrotal swellings. The other scrotal swellings seen were either due to fluid passing through a patent processus vaginalis (blood, chyle, or parenteral feeding fluid) or scrotal surgery. There were nine cases seen of idiopathic scrotal oedema but they were all over the age of 5 years. We did not see the variety of scrotal swellings due to medical causes—for example, Henoch-Schonlein syndrome—that are reported in other series

Conclusion

Scrotal swelling is a common condition in boys under the age of 5, with a wide range of diseases Only by careful history taking and examination and a very high level of suspicion will the less common and more serious conditions be diagnosed and treated promptly.

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Growth hormone response to a standardised exercise test in relation to puberty and stature

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SUMMARY Growth hormone (GH) was measured before and 10 minutes after a standardised bicycle exercise test (duration 15 minutes) in 37 short children (group 1: mean (SD) age 12·8 (3·5) years; mean (SD) bone age 10·4 (3·6) years; mean (SD) height standard deviation score (SDS) −2·8 (0·7)), 16 tall children (group 2: mean age 12·9 (2·8) years; mean bone age 13·9 (1·4) years; mean height SDS 3·0 (0·8)), and 30 normal children (group 3: mean age 13·3 (3·2) years; mean bone age 12·8 (3·4) years; mean height SDS −0·4 (0·8)). Results of GH are expressed as mean (SEM).

The pre-exercise GH was similar in the three groups (group 1, 8·0 (2·3) mU/l, group 2, 8·5 (2·5) mU/l, and group 3, 8·3 (2·3) mU/l). There was a significant rise in GH after exercise in all three groups. GH after exercise was higher in group 2 (35·1 (2·5) mU/l) compared with groups 1 and 3 (17·8 (3·0) and (20·8 (3·2) mU/l). Post-exercise GH was <10 mU/l in 29 children (34% total; 49% group 1, 6% group 2, and 34% group 3). There was a positive relation between post-exercise GH and both bone age and pubic hair stage. Multiple regression analysis revealed that relevant predictors of a rise in GH with exercise were different for the sexes in these children with varying stature: for boys, bone age and pubic hair stage; for girls, height and height SDS. All the tall girls were in puberty. No statistical relation was observed between post-exercise GH and cardiovascular response to exercise, time of day of exercise, time of eating before exercise, and plasma insulin or insulin to glucose ratio at time of exercise. We conclude that the GH response to the physiological stimulus of exercise is higher in puberty compared with childhood. Therefore, although children may be suspected of having GH deficiency after a failure of GH to increase after exercise, a non-response may be a normal finding in prepubertal children, independent of stature.

The growth hormone (GH) response to the physiological stimulus of exercise is advocated as part of the investigation of growth disorders in children.[1–8] As in pharmacological and other physiological tests of GH secretion, however, the stimulus of exercise may fail to induce a significant rise in plasma GH concentration.[9] Studies investigating the factors that influence GH response to exercise have concentrated on the standardisation of the exercise test and the degree of work performed by the subject. Even with attention to these details, there is still a high percentage of children with no rise in GH with exercise—that is, a false no response. We therefore investigated factors that influence the GH response to exercise by measuring GH before and after a standardised exercise test in short and tall children and compared this response with that seen in children of normal stature.

Patients and methods

Eighty three children (49 boys and 34 girls) were investigated. Group 1 consisted of 37 short children (27 boys and 10 girls) with constitutional growth delay, defined as height <3rd centile with a height velocity at the 50th centile for age (according to data from the Zurich longitudinal growth study). (Prader A, Issler C, Molinari L, Largo R. Body measurements, growth measurements and bone age of healthy children, Unpublished data.) Group 2 consisted of 16 tall children (eight boys and eight girls) whose height was >97th centile Group 3 consisted of 30 children of normal stature (14 boys and 16 girls) whose height was between the 3rd and 97th centiles; 20 were friends or siblings of children in groups 1 and 2, and 10 were children under investigation for other endocrine problems but in

Table 1 *Chronological age, bone age, and height standard deviation score (SDS) in group 1 (short children), group 2 (tall children), and group 3 (children of normal stature). Values are mean (SD)*

	Chronological age (yrs)	*Bone age (yrs)*	*Height SDS*
Group 1 (n=37)	12·8 (3·5)	10·6 (3·8)	−2·6 (0·8)
Group 2 (n=16)	12·9 (2·8)	14·1 (1·6)	3·2 (0·9)
Group 3 (n=30)	14·4 (2·7)	12·8 (3·4)	−0·5 (0·8)

Table 2 *Growth hormone (mU/l) before and 10 minutes after exercise (15 minutes' duration) in group 1 (short children), group 2 (tall children), and group 3 (children of normal stature). Values are mean (SEM)*

	Pre-exercise	*Post-exercise*
Group 1	8·0 (2·3)	17·8 (3·0)
Group 2	8·5 (2·5)	35·1 (2·5)
Group 3	8·3 (2·2)	20·8 (3·2)

whom growth was normal. Informed consent was obtained from the children and their parents before the test. Puberty in each child was assessed according to Tanner.[10] Mean chronological age, bone age (Greulich and Pyle[11]), and height standard deviation score (SDS) for each group is shown in Table 1.

Each child performed a 15 minute standardised incremental workload test using a bicycle ergometer (Puch Tunturi). In the first five minutes of the test the child exercised at a constant work load of 1 watt/kg, in the second five minutes at 1·5 watts/kg, and in the final five minutes at 2 watts/kg. At the end of the exercise period the pulse rate was counted. All children completed the exercise test. The youngest child was 5·3 years of age and the shortest child 100·2 cm in height.

Blood samples were taken from 75 of the children (90%) before the exercise test and from all of the children 25 minutes after the start of the exercise. Group 1 had blood taken at more frequent intervals: 0, 5, 10, 15, 25, 45, and 60 minutes from the start of exercise. From each blood sample blood glucose (mmol/l), plasma insulin (pmol/l), and plasma growth hormone (mU/l) were measured according to our laboratory methods.[12]

Statistical differences comparing pre- with post-exercise GH were calculated by a paired Wilcoxon test. Statistical differences of post-exercise GH within the three groups were calculated by the non-parametric ranked analysis of variance according to Kruskall and Wallis. Statistical differences in prepubertal post-exercise GH compared with pubertal values were calculated by a Mann-Whitney test. Calculation of relevant predictors of the post-exercise GH response was performed by multiple regression analysis.[13]

Results

The plasma concentration of GH pre- and post-exercise is given in Table 2. Results are expressed as mean (SEM).

Pre-exercise GH was similar in all three groups. There was a significant increase in GH with exercise in all three groups (Δ GH: group 1, 9·8 (2·7) mU/l, group 2, 26·6 (2·5) mU/l, and group 3, 12·5 (2·7) mU/l; $p<0·001$). This rise in GH with exercise remained significant on separation of the groups by sex, with the exception of short girls (group 1 girls). Post-exercise GH was significantly higher in group 2 compared with groups 1 and 3 ($p<0·005$). Separation of the groups by sex revealed no significant differences in boys in post-exercise GH (group 1, 19·0 (3·6) mU/l, group 2, 27·1 (3·1) mU/l, group 3, 22·9 (4·7) mU/l) but a significantly higher GH in tall girls (group 1, 14·5 (5·7) mU/l, group 2, 43·0 (8·9) mU/l, and group 3, 18·9 (4·5) mU/l; $p<0·025$).

In the seven children from group 1 who had blood taken more often during and after exercise GH peaked between 15 and 25 minutes. At 0 minutes mean GH measured 3·9 mU/l, at 5 minutes 5·0 mU/l, at 10 minutes 9·7 mU/l, at 15 minutes 16·0 mU/l, at 25 minutes 16·0 mU/l, at 45 minutes 10·0 mU/l, and at 60 minutes 3·3 mU/l, respectively.

Post-exercise GH was <10 mU/l in 29 children (34% total; 49% group 1, 6% group 2 and 34% group 3). No significant relations were observed between post-exercise GH and time of day of exercise, time of last meal in relation to exercise test, plasma insulin or insulin to blood glucose ratio, or cardiovascular response to exercise. All children had a pulse rate above 160 beats/min at the end of the exercise, with 85% having a pulse rate >200.

There was a positive relation between post-exercise GH and both bone age ($p<0·05$) and pubic hair stage ($p<0·05$); this was also present on separation of the groups by sex (Figs. 1 and 2). Post-exercise GH was significantly higher with advancing bone age and in post-puberty compared with prepuberty: GH at bone age <10 years was 13·8 (2·8) mU/l and at bone age >10 years was 25·3 (2·7) mU/l ($p<0·01$); GH at pubic hair stage P1 was 12·8 (2·2) mU/l and at P3–5 was 31·4 (3·4) mU/l ($p<0·05$). Multiple regression analysis revealed that the relevant predictors of a rise in GH with exercise was different for the sexes: for boys, the predictors were bone age and pubic hair stage ($p<0·001$); for girls, the predictors were height and height SDS

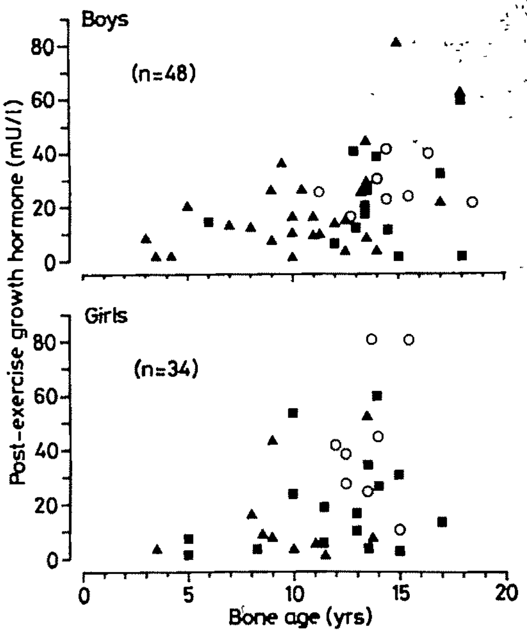

Fig 1 *The post-exercise growth hormone response (10 minutes after a 15 minute exercise period) related to bone age in group 1 (short children) (▲), group 2 (tall children) (○), and group 3 (children of normal stature) (■)*

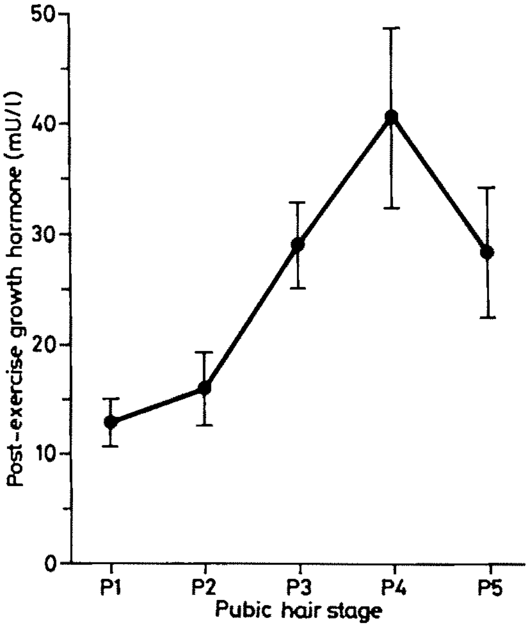

Fig 2 *The post-exercise growth hormone response (10 minutes after a 15 minute exercise period) related to pubic hair stage according to Tanner[10] in children of varying stature. Data for boys and girls combined*

($p<0\cdot001$). All the tall girls and five of the eight boys were in advanced puberty.

Discussion

The post-exercise GH concentration after a standardised exercise test showed considerable variation in children with differing stature. One third of the children had a 'false no response' result, with post-exercise GH <10 mU/l. Failure to detect a rise in GH after the exercise could be accounted for by the use of a single blood test taken 10 minutes after the exercise, which may miss a rise in GH. Previous studies have shown this, however, to be the time of the peak response of GH to exercise,[1 14 15] and this was confirmed in the seven children from group 1 who had blood samples taken at more frequent intervals.

The degree of physical work performed during the exercise test is a factor known to influence the GH response to exercise. Prolonged mild exercise and severe maximum exercise have both been shown to be poor stimuli of GH; a submaximal workload test, exercising to roughly 70% of maximum oxygen capacity, with the exercise period limited to between 10–20 minutes, seems optimal in inducing a rise in GH.[1] In this study the exercise period was 15 minutes and a rise in the pulse rate to >160 beats/min suggests that an oxygen uptake in the order of 70% was achieved,[16] even in the face of the expected variation in physical fitness of the children.

No relation was observed between the post-exercise GH response and time of day at which the exercise was performed (all tests being performed between 0800 and 1700h) and in the timing of the meal previous to the exercise. Insulin and blood glucose concentrations at the time of the exercise also had no relation to the GH response.

The development of puberty influenced the GH response to exercise. The older the bone age and the further the stage of pubic hair development the higher the post-exercise GH concentration The relevant predictors of GH response were different in the groups of children when separated by sex: multiple regression analysis confirmed bone age and pubic hair stage as the relevant predictor in boys but suggested that stature was the relevant predictor in girls Height, age, bone age, and pubic hair stages themselves were correlated with the pubertal growth spurt, and this would seem to account for the higher GH in tall children in comparison with other children. The apparent excessive GH response in tall girls, however, is not completely explained. It is interesting to note that tall girls in puberty have been reported as showing a 'paradoxical' GH response to oral glucose[17] and thyrotrophin releasing hormone.[18] It remains to be seen if a high GH response to physiological and pharmocological testing indicates a pathological cause of tall stature in tall girls or if they are being investigated at the point of puberty where GH response would be expected to be maximal.

Age related changes in the spontaneous secretory rate and pattern of GH have been reported previously. Changes have been seen in response to pharmacological testing, as well as in the physiological tests of sleep and exercise.[19-22] Twenty four hour measurements of GH have shown a change in secretory pattern from prepuberty to adolescence.[23] Enhancement of GH secretion to pharmacological tests by either testosterone[24] or exercise is higher in puberty compared with childhood. Therefore, although children may be suspected of having GH deficiency after a failure of GH to increase with exercise, a non-response may be a normal finding in prepubertal children, independent of stature.

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Growth and growth factors in diabetes mellitus

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SUMMARY Growth of 79 children with diabetes was analysed at diagnosis and again after one to 10·7 years of treatment with insulin. Both sexes were tall at onset, whereas at the last observation boys alone showed significant growth retardation. Height standard deviation score (SDS), however, showed no significant fall either in 32 subjects reassessed after five years of disease or in 18 subjects examined at full stature. Skeletal maturity was not significantly impaired after treatment. Pubertal growth spurt was reduced, especially in girls and in subjects with onset of disease at or around puberty. We found no significant correlation between height and height velocity SDS and glycosylated haemoglobin values or secretion of growth hormone during the arginine test. Somatomedin C values were correlated with height velocity SDS in prepubertal boys. The results of this study suggest that there are interferences in the growth of children with diabetes but that they do not seem to have a significant influence on adult height.

It is well recognised that growth is seriously impaired in cases of very poorly controlled diabetes.[1] What is less certain, however, is whether diabetes influences growth or limits adult height in children treated conventionally in whom the disease is fairly well controlled—that is, most cases today.

There are some discrepancies in the findings of various authors who have published papers on this subject. Tattersall *et al* found that in patients with type 1 diabetes there was a decrease in adult height compared with their identical non-affected twins [2] Growth delay was also observed by Jivani *et al*[3] and Edelsten *et al*,[4] while according to Birkbeck,[5] Rudolf *et al*,[6] and Jackson[7] children with a fairly high degree of metabolic control showed normal growth rate.

The methods used in these studies vary, however, and are questionable as regards the way in which growth delay was calculated, the type of follow up used, and the methods used for assessing diabetes control.

This study reports our experience with a group of children with diabetes followed longitudinally from the onset of disease. In these subjects height and height velocity were evaluated as standard deviation scores (SDS) and control of the disease as total glycosylated haemoglobin (HbA_{1C}).

Further, in these subjects growth rate was compared with secretion of growth hormone and plasma somatomedin C concentrations

Patients

Seventy nine subjects (35 boys and 44 girls, with 58 prepubertal and 21 pubertal) with type 1 diabetes mellitus, aged 0·7–14·8 years (mean (SD) 7·44 (3·56) years) were examined at the onset of disease. These subjects were observed over a period of one to 10·7 years (mean (SD) 4·48 (2·59) years), 32 (18 girls and 14 boys) have been followed longitudinally for at least five years.

At the onset of disease and at each subsequent control (three or four times a year) the following details were evaluated in each child: height as centile and as SDS, pubertal stage, bone age (in 66 cases), and control of the disease by HbA_{1C} assay. During this entire period of observation mean (SD) HbA_{1C} was 11·17 (1·31)% for boys and 11·96 (1·81)% for girls. We considered subjects with HbA_{1C} values <10% as having good control, those with HbA_{1C} values between 10 and 12% as having fair control, and those with values >12% as having poor control.

Height velocity was calculated annually as SDS. Somatomedin C basal values were determined in 43 subjects, and 72 also had an arginine test to evaluate growth hormone Overall secretion of growth hormone was evaluated as the integrated area of the curve.

During the observation period, 26 subjects (nine boys and 17 girls) entered puberty, while 18 subjects (10 boys and eight girls) reached adult height.

Methods

Tanner's centiles[8] were used in the evaluation of height and height velocity.

Height and height velocity SDS were calculated according to the formula $\frac{Xi-Mx}{Sx}$ where Xi is the actual measurement, Mx is the mean (50th centile) of subjects of the same chronological age, and Sx is the standard deviation corresponding to that age. In those cases where bone age was delayed or advanced by more than one standard deviation compared with chronological age SDS referred to bone age.

Pubertal stage was evaluated according to Tanner[9] and bone age according to Greulich and Pyle's atlas.[10]

HbA_{1C} was assayed with Trivelli's method (BIORAD Column Method)[11] and growth hormone by radioimmunoassay. Somatomedin C was measured by radioimmunoassay (RIA kit; Nicholas Institute Products, San Juan Capistrano, California, United States) in accordance with the method of Furlanetto *et al*[12] The intra- and interassay variabilities were 5% and 10%, respectively. The 'r' correlation coefficient, Student's *t* test, paired *t* test, and χ^2 test were used for statistical analysis of the data.

Results

Height. Figures 1 and 2 and Table 1 show the height distribution of all the subjects, both at onset of disease and at the last observation. From Table 1, it is evident that at the onset of disease most of the boys and girls were tall and that the number of boys whose height was over the 50th centile was significantly ($p<0{\cdot}05$) greater at the onset of disease than after treatment.

Table 2 shows the mean centiles and height SDSs both at the onset of disease and at the last observation. Height SDS in the boys was significantly ($p<0{\cdot}0025$) higher at the onset of disease than after treatment.

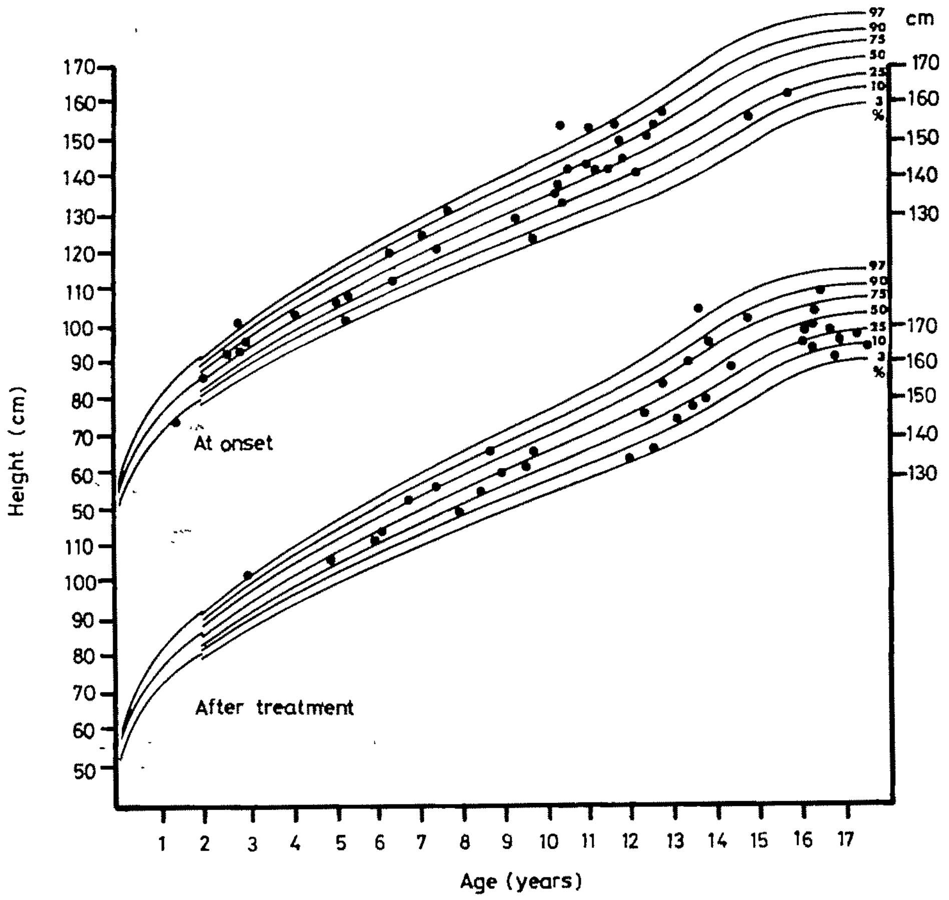

Fig. 1 *Height at onset of disease and after treatment in 35 boys with insulin dependent diabetes mellitus*

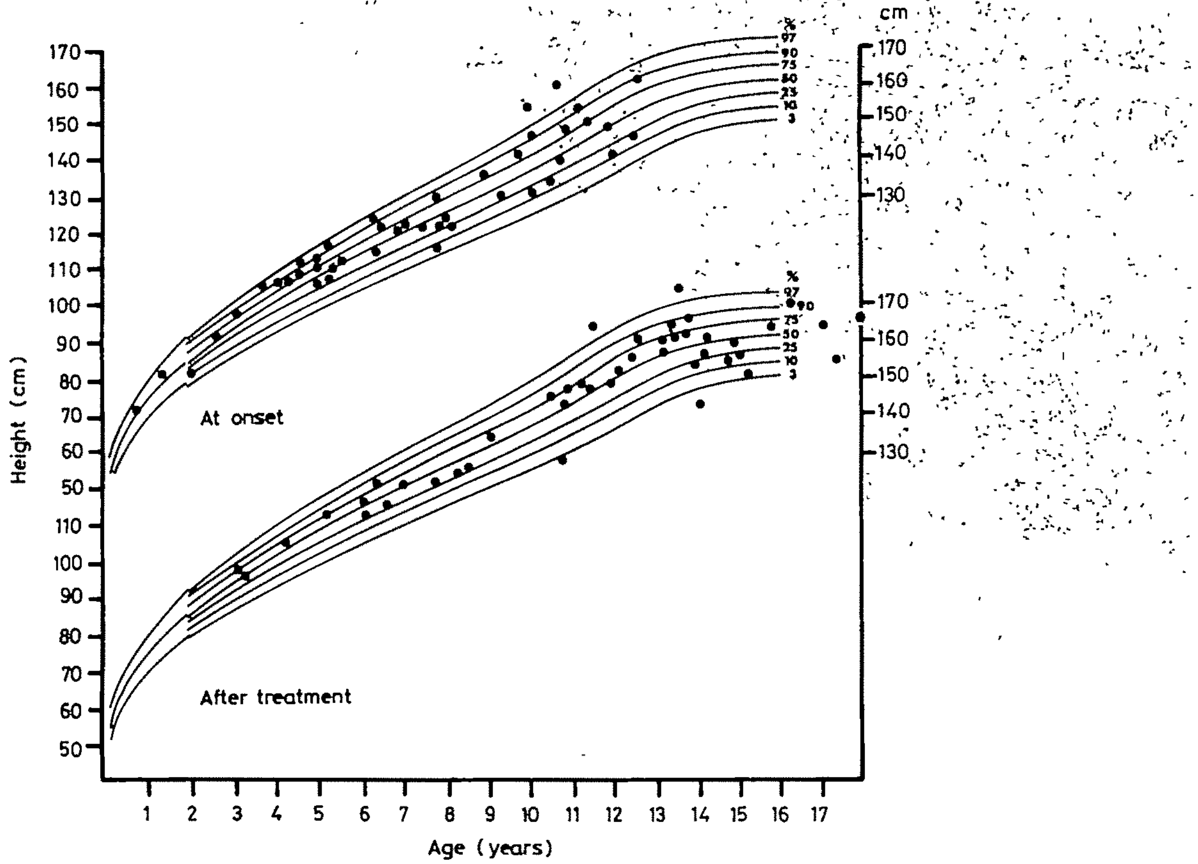

Fig. 2 *Height at onset of disease and after treatment for 44 girls with insulin dependent diabetes mellitus.*

As the period of treatment in these subjects varied considerably we subsequently made this variable uniform, taking into consideration only those patients (32 cases, 14 boys and 18 girls) observed during their first five years of disease. The data referring to these subjects are reported in Table 3. Analysis of these data (paired *t* test) indicated no differences between SDS values at the onset and in the fifth year of disease.

Table 1 *Height at onset and after treatment in children with insulin dependent diabetes mellitus*

	No of cases	
	≥50th centile	*<50th centile*
Boys (n=35)		
At onset	21	14
After treatment	12*	23
Girls (n=44)		
At onset	28	16
After treatment	29	15

*χ^2=4 64, p<0 05

Table 2 *Mean (SD) height centile value and height standard deviation score (SDS) at onset and after treatment in 35 boys (M) and 44 girls (F) with insulin dependent diabetes mellitus*

	Sex	*At onset*	*After treatment*
Height centile value	M	53 63(26 60)	45 48(29 45)
	F	57 93(27 36)	54 72(27 79)
Height SDS	M	+0 46(1 32)	−0 40(0 99)*
	F	+0 49(1 30)	+0 002(1 03)

*p<0 0025 *v* Height SDS at onset

Table 3 *Mean (SD) height centile value and height standard deviation score (SDS) at onset and after five years of treatment in 14 boys (M) and 18 girls (F) with insulin dependent diabetes mellitus*

	Sex	*At onset*	*After five years of treatment*
Height centile value	M	49 06(25 82)	31 20(24 67)
	F	63 10(23 92)	57 14(25 62)
Height SDS	M	+0 66(1 66)	−0 37(1 32)
	F	+0 86(1 05)	+0 052(1 05)

Examination of those subjects who reached full stature during follow up (10 boys and eight girls) showed that the initial mean of the SDS values was not significantly different from the final mean for either boys or girls (Table 4).

Skeletal maturity. The bone age mean, both at the onset of disease and after treatment, did not differ from the chronological age mean (Table 5).

The percentage of subjects with bone age delayed or advanced more than one standard deviation was not significantly different either before or after treatment

Height velocity. The mean velocity SDS decreased progressively during the first years of disease only in those subjects who were pubertal from onset.

Patients with onset at least three years before puberty showed a growth spurt that was slightly lower than the mean and not delayed This was especially so in the girls (Fig 3). On the contrary in those patients with onset at or around puberty the spurt, which had already begun, seemed to be interrupted suddenly (Fig 4).

Table 4 *Mean (SD) height standard deviation score at onset and at full stature in 18 patients with diabetes*

	At onset	At full stature
Boys (n=10)	+0·10(0 60)	−0 50(0 90)
Girls (n=8)	+0 11(1 64)	+0 03(1 63)

Table 5 *Skeletal maturity at onset and after treatment in 30 boys (M) and 36 girls (F) with diabetes*

	Sex	At onset	After treatment
Mean (SD) chronological age	M	8 05(4 04)	12 34(4 14)
(yrs)	F	7·23(2 94)	11 76(3 59)
Mean (SD) bone age (yrs)	M	7 75(4 68)	12 00(4 50)
	F	7 66(3 38)	12 14(3 41)
% Cases with advanced	M	10 0	10 7
skeletal maturation	F	16 6	18 7
% Cases with delayed	M	20 0	21 4
skeletal maturation	F	8 4	3 1
% Cases with normal	M	70 0	67 9
skeletal maturation	F	75 0	78 2

Puberty. The data referring to puberty are summarised in Table 6.

Metabolic control. We found no significant correlation between mean HbA_{1C} values obtained over the entire observation period and either height SDS score, values of the difference in the scores before and after treatment, or velocity SDS.

If mean HbA_{1C} values are evaluated by year of disease a significant positive correlation ($p<0\cdot01$) is found only in the second year of disease between HbA_{1C} values and velocity SDS. The height and height velocity SDS means were no different in subjects with good, fair, or poor control.

Growth hormone and somatomedin C. Somatomedin C values and secretion of growth hormone during the arginine test did not seem to be significantly correlated either with height SDS, velocity SDS, or HbA_{1C} values. Somatomedin C values were, however, positively correlated with velocity SDS ($p<0\cdot05$) only in prepubertal boys

As reported in one of our previous papers[13] it was only in prepubertal subjects that means somatomedin C values seemed to be significantly lower than in the respective control children.

Using the 274 control subjects examined in our previous study,[14] we subdivided our subjects according to whether somatomedin C values were lower, greater, or within one standard deviation of the mean of subjects of the same sex and pubertal stage.

In boys, both pubertal and prepubertal, height

Table 6 *Pubertal development in girls and boys with insulin dependent diabetes mellitus Values are mean (SD) (range)*

	Boys		Girls		
Onset of puberty (yrs)	11 33(1 18) (9 50–14)	(n=20)	10 92(1 13) (9–13 91)		(n=24)
Age at menarche (yrs)	—		12 93(1 18) (10 25–15 16)		(n=20)
Full stature age (yrs)	17 73(2 1) (15 16–21 83)	(n=14)	16 00(1 89) (13 25–19 58)		(n=15)
Growth rate from onset of puberty to full stature (cm)	28 07(6 4) (20 45–39)	(n=7)	14 91(3 93) (8 86–21 64)		(n=13)
			B_2→ menarche	10 80(4 62) (4 21–21 23)	(n=18)
			Menarche→full stature	4 16(2 67) (1 32–10 54)	(n=12)
Duration of puberty (yrs)	6 58(1 66) (4 75–8 83)	(n=7)	4 57(1 82) (2 52–6 42)		(n=13)

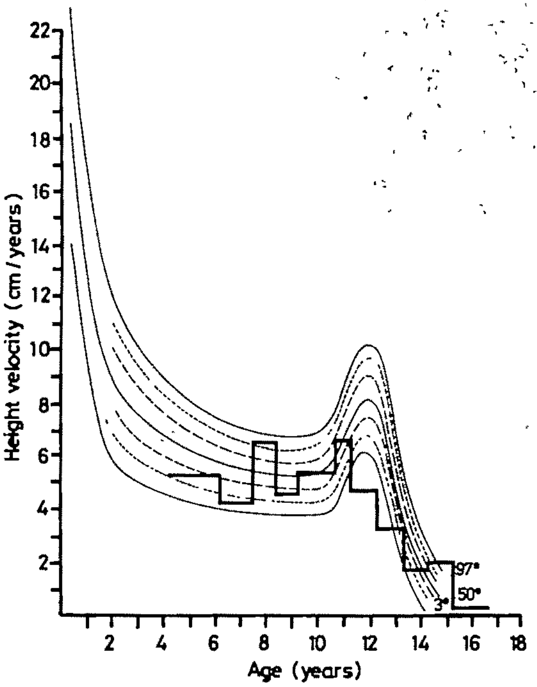

Fig. 3 *Height velocity mean in 12 girls with onset of disease at least three years before puberty*

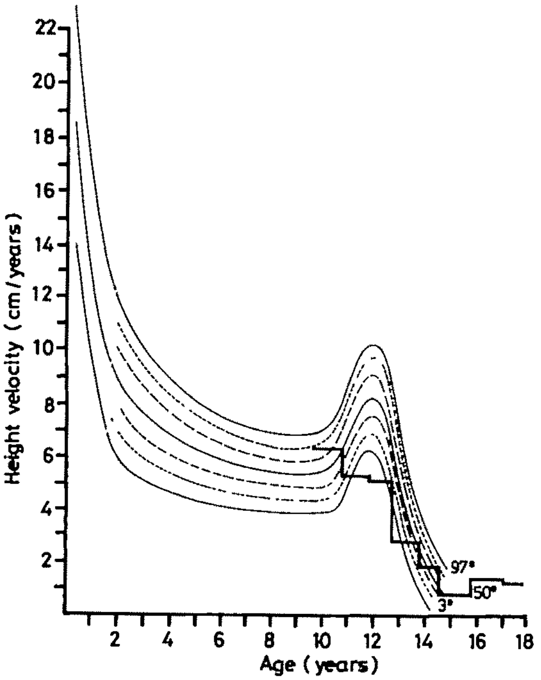

Fig 4 *Height velocity mean in 13 girls with onset of disease at or around puberty.*

and height velocity SDS were higher in subjects whose somatomedin values were greater by one standard deviation than in those subjects whose somatomedin C values were lower or within one standard deviation.

Discussion

The patients with diabetes in this study were taller than average at the onset of disease This confirms the data reported by Edelsten *et al* [4]

Like these authors, we too used the population charts of Tanner and Whitehouse for height as no standards are available for the height of children in our area. Our preliminary data, however, suggest that the height of our healthy children does not differ greatly from that observed by Tanner and his colleagues. It has been hypothesised that the advanced growth of children with diabetes at the onset of disease might be the result of the anabolic activity of insulin, which may exist in abnormal quantities for some time before the clinical onset of diabetes.[3 4]

Our results concerning height after treatment, however, cannot be interpreted so easily. If, like many authors,[3–5] we use a cross sectional method—that is, examining all subjects at their most recent measurement, independently of duration of disease—we find that there is an excess of boys shorter than the mean. If, however, we use a longitudinal method and take account of adult height, although the number of subjects may be small, the differences encountered with the cross sectional method are no longer found.

Given the importance of puberty in determining adult height, we followed other authors[3] and examined the growth of children with diabetes during this period. According to Jivani *et al* growth rate is normal until puberty, which is exactly when it is impaired [3] These authors state that the pubertal growth spurt is reduced and also delayed among girls only when the onset of disease is well before puberty. This does not agree with our data, but the discrepancy is not easy to interpret as Jivani *et al* gave no numerical data in their paper. Our patients had a pubertal spurt that was never delayed but was reduced. This occurred more in girls than in boys and also in those with onset of disease around puberty rather than in those with onset well before puberty (Figs. 3 and 4).

Furthermore, we have been unable to indicate any relation between metabolic control and growth data. Paradoxically, as reported by Jivani *et al*,[3] the more poorly controlled our patients were at the second year of disease the better they seemed to grow

Other studies, however, have come to the opposite conclusion.[6,7] Rudolf *et al* found that growth rate, which was already normal, had doubled in nine adolescents with diabetes receiving intensive treatment (insulin pump or multiple injection) for six months and whose metabolic profile had shown a pronounced improvement.[6]

As regards the time when pubertal development begins and ends, we used the data published by Pezzini *et al*[15] as we have none of our own referring to the healthy population. These authors state that healthy girls begin pubertal development at 10·60±0·84 years and have the menarche at 12·50±0·80 years. Our data indicate that girls with diabetes are about six months behind these averages, while the data of Pezzini *et al* indicate a delay of one year.[15]

That there were no significant delays in sexual maturity was also suggested by our data concerning skeletal maturity, which, during treatment, followed the physiological pattern Birkbeck reached the same conclusions concerning skeletal maturity,[5] while Edelsten *et al* reported advanced skeletal maturity at onset of disease and a clear decrease in skeletal maturity SDS after treatment only in boys.[4]

Finally, growth hormone concentrations do not seem to interfere with growth or to be influenced by metabolic control. It is worth remembering, however, that these data refer to a precise moment in the history of the disease and therefore, given the extreme variability of secretion of growth hormone in the same subject, it cannot be ruled out that these data might have been different at another time.

Somatomedin C seems to behave differently in the two sexes While it seems to have no relation to growth characteristics in girls, in boys the relation seems to be very definite. In boys, in fact, the higher the somatomedin C values the better the growth rate. Further, in prepubertal boys there is a significant correlation between somatomedin C concentrations and velocity SDS.

We conclude that there seem to be interferences in the growth rate of children and adolescents with diabetes and that they are evident in particular as a decrease in pubertal spurt independent of metabolic control and conditioned, in boys, by production of somatomedin C. These interferences do not seem to have a significant influence on adult height

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Childhood asthma and growth outcome

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SUMMARY To study the ultimate growth variables of children with asthma we analysed the military medical records of 54 041 boys and 38 102 girls at the age of 17 years. History of asthma was found in 2252 boys and 1158 girls, who were then categorised according to three grades of severity. Analysis of their growth was made separately for each sex and for each grade of severity of clinical disease.

Boys who suffered from mild asthma that subsided before adolescence were significantly taller, heavier, and fatter than their respective controls. There was a slight decrement in all three growth variables in correlation with increased severity. The most severely affected patients had retarded height and weight in comparison with the mildly affected children, but the differences were not significant. The same tendency was found in the girls.

Children with asthma will ultimately reach normal height and weight. Those who are mildly affected tend to be even taller and heavier than adolescents without asthma The severity of the asthma influences final growth.

Children suffering from asthma can show growth retardation both in height [1–7] and maturation.[8] It has been further suggested that the retarded bone age of most children with severe asthma indicates that they will tend to mature late[9] and will ultimately grow to a normal height

The purpose of this study was to study the growth variables (height, weight, and body mass index) of children with asthma at the age of 17 years.

Patients and methods

We studied the military medical records of 54 125 boys and 38 185 girls who were examined at the age of 17 years as part of a routine health assessment in the Israeli defence forces conscription

Each adolescent underwent a complete physical examination Growth variables that were studied included height, weight, and body mass index (body mass index=weight/height^2)

Adolescents who suffered from bone diseases that might have any influence on growth outcome (severe scoliosis, neuromuscular or bone diseases, neurofibromatosis, etc) were excluded, and thus 54 041 boys and 38 102 girls were left in the study.

As part of the health assessment each adolescent was asked whether he had ever suffered from asthma or any other respiratory disease. Any positive information was confirmed by a letter from the family physician, and the severity of asthma was then categorised according to the following criteria.

Grade A: Recurrent episodes of asthma during childhood; remission of symptoms for over three years.

Grade B: Active asthma without constant or preventive treatment.

Grade C. Active asthma that demanded constant preventive medicine, including sodium cromoglycate, bronchodilators, and inhalation of steroids. A number of children in each group had been given treatment for asthma, including systemic steroids, during childhood

As the growth variables studied differed according to sex and ethnic groups in Israel the analysis was made separately for each of the six most common ethnic groups. Statistical analysis was made using the Student's t test and χ^2 test.

Results

The Table depicts the number of adolescents studied with (total and for each grade of severity) and without asthma according to sex and parental origin The incidence of asthma ranged from 2·3–5·9% for boys and 1·6–3·9% for girls A significantly ($p<0·001$) lower incidence of asthma was found in

Table *No of adolescents with (total and for each grade of severity) and without asthma according to parents' origin and sex*

Parents' origin	*Adolescents without asthma*		*Adolescents with childhood asthma*					
			Grade A		*Grade B*		*Grade C*	
	M	F	M	F	M	F	M	F
West Europe	12618	10685	286	151	341	190	168	96
East Europe	3974	2632	54	35	81	38	43	26
Iraq	5317	4111	113	53	97	46	46	19
Yemen	3611	2128	59	33	53	29	34	14
Morocco	9839	6544	111	49	82	39	34	18
Others	16427	10242	292	132	242	135	116	55
Total	51789	36944	315	453	896	477	441	228

boys and girls whose parents originated from Morocco (2·3% and 1·6%, respectively) and a higher incidence ($p<0{\cdot}001$) in both sexes from west Europe (5·9% and 3·9%, respectively)

Figure 1 depicts the mean (SEM) height, weight, and body mass index, respectively, of the children with asthma in comparison with the controls. Boys with mild asthma (grade A) were significantly taller ($p<0{\cdot}05$), heavier ($p<0{\cdot}01$), and fatter ($p<0{\cdot}01$) than their respective controls. The height of adolescents with moderate asthma (grade B) was also significantly higher ($p<0{\cdot}05$) than their controls. There was a slight decrease in all the growth variables studied in correlation with the severity: the most severely affected children had retarded growth in height and weight in comparison with mild cases. Although the same tendency was found for the girls, the differences were not significant. Figure 2 shows the heights of the children with asthma and the controls according to their ethnic origin. The results obtained were similar to those reported above for most ethnic groups, although the differences were not significant (except for the children with mild asthma who originated from east Europe). Analysis of the weight and body mass index according to the parents' origin did not reveal significant differences between the children with and without asthma.

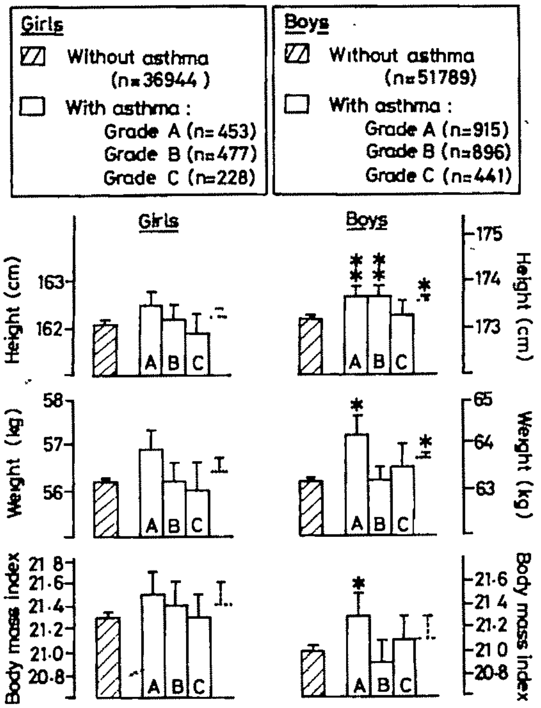

Fig. 1 *Mean (SEM) height, weight, and body mass index of boys and girls with asthma (grades A, B, and C) in comparison with their controls (dotted lines represent the mean of the three grades of asthma)*

*p<0 05, **p<0 01

Discussion

Our study suggests that although children with asthma have retardation of growth[1–7] and maturation,[1 8] they will ultimately grow to normal height and weight. Of interest is the observation that children with mild asthma tend be become even taller and heavier than children who have not had asthma. As children who mature late are likely to present a slightly taller adult stature when compared with those who mature early[10 11] the fact that children with asthma often have delayed bone age and adolescence[1 9] may be the reason for their slightly taller stature. We have not tested whether this observation in our group with asthma was due to an eventual socioeconomic selection; as this difference was observed in all the ethnic groups studied, however, it seems less likely that this is the reason. Asthma is not considered to be related to socioeconomic state.[1]

It has been shown previously that a relation exists between the severity of symptoms of asthma and the degree of growth retardation.[1 12] Our study suggests

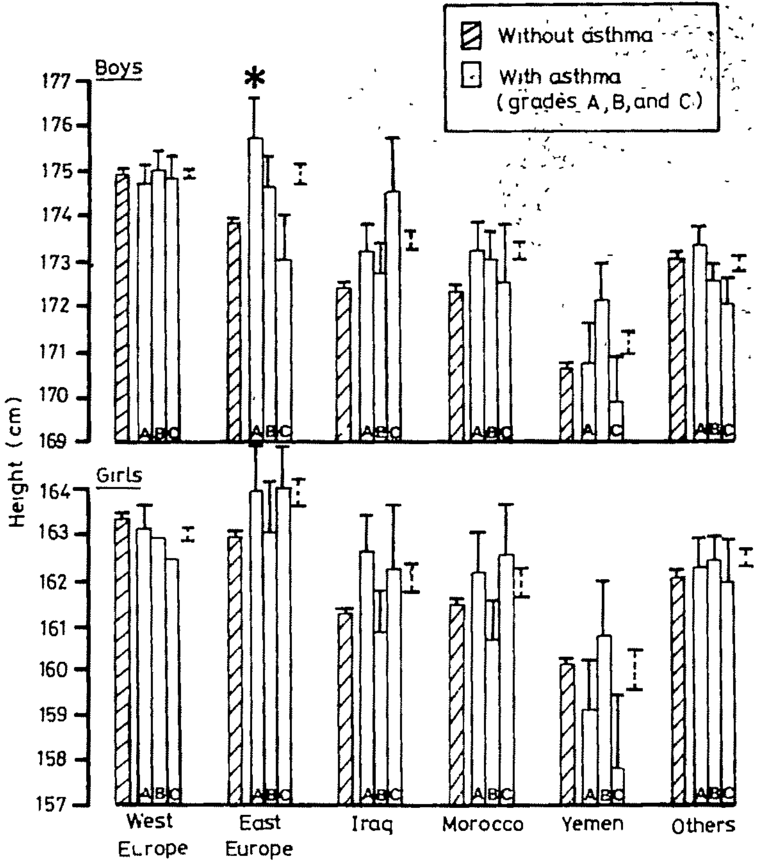

Fig. 2 *Comparison between height (mean (SEM)) of adolescents with and without asthma (grades A, B, and C) for parents' origin and sexes (dotted lines represent the mean height of the three grades of asthma).*

$^*p<0{\cdot}05$

that the severity of the asthma also influences the final growth. Most severely affected patients had retarded growth in height and weight in comparison with the mildly affected children

We are grateful to Professor A Perzelan, Professor J Kark, and B Lederman for their help

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Symptoms, atopy, and bronchial response to methacholine in parents with asthma and their children

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SUMMARY We have studied 50 children with one parent with asthma at a mean age of 6·4 years by symptom questionnaire and performed allergy skin testing and measurement of bronchial responsiveness to methacholine in both parent and child in 29–32 cases. Ninety eight per cent of the parents were receiving medication for asthma. Fifty one per cent had visited their doctor and 20% had taken more than five days off work in the previous 12 months; 12% had been admitted to hospital during the preceding 10 years. In the children the prevalences of wheeze, shortness of breath, and cough were all about double that found in a general population survey of children of similar age. Atopy was present in 90% of parents, but the prevalence of atopy among the children was not significantly different from the children in the general population. Eczema and hay fever, however, had high prevalences of 40% and 24%, respectively. Responsiveness to methacholine (provocation dose achieving 20% fall in forced expiratory volume in one second <6·4 µmol) was found in 93% of parents and 45% of children, which is compatible with a large increase compared with the general population. All atopic but only 50% of non-atopic children with symptoms of asthma responded to methacholine.

These findings indicate that children who have one parent with asthma have roughly double the chance of developing clinical features of asthma compared with the general population and suggests that, in these children, a causal interaction occurs between atopy and bronchial hyper-responsiveness.

Bronchial asthma is a disease with a reported current prevalence in adults of 1·2–6·2% in the western world.[1] Recent work in the United Kingdom has shown that prevalence figures of between 10% and 12% are more realistic for schoolchildren under the age 10 [2 3] The derivation of figures for the prevalence of asthma assumes, however, a precision of diagnosis and definition that does not exist for this disease.[4] In an attempt to overcome this problem some workers have described prevalence figures for a single symptom, such as recurrent wheeze.[3]

One of the major pathophysiological features of asthma is the presence of enhanced responsiveness of the airways to a wide range of specific and non-specific stimuli—bronchial hyper-reactivity or hyper-responsiveness. Non-specific bronchial responsiveness may be quantified in the laboratory by provocation testing with agents such as histamine, methacholine, and cold air[5–7] and is closely related to symptomatic bronchial irritability characterised by symptoms of wheeze, cough, dyspnoea, or chest tightness in response to a variety of environmental factors.[8]

A common aetiological factor proposed for asthma in older children and young adults is atopy defined by skin prick testing to common environmental allergens and the presence of associated allergic disease, such as eczema, rhinitis, urticaria, and food allergy.[8] It has been suggested that atopy may enhance the expression of an independently inherited tendency to develop asthma.[9] In support of this hypothesis studies have indicated that, in susceptible individuals, environmental exposure to common allergens, such as grass pollen and house dust mite, enhances bronchial responsiveness to histamine and methacholine at the same time as precipitating symptoms of asthma[10] and that removal from the offending allergens reverses the process.[11]

Several family and twin studies have shown a familial component in the aetiology of the atopic illnesses[9 12 13]—asthma, eczema, and hay fever. So far, however, there has been no prospective investigation to determine the extent of this relation. In this paper we describe a study involving a cohort of children who had one parent with asthma in which we compared the range of respiratory symptoms with atopic state and measurement of bronchial responsiveness to methacholine.

Patients and methods

Patients. The original cohort of 100 children, with a family history of asthma, was collected from an antenatal clinic between 1977 and 1979 for a study of respiratory syncytial virus infection and maternal antibody concentrations.[14] All children in the cohort had a first degree relative with asthma, and in 89 children this consisted of one parent with asthma; the other 11 children were excluded from this study A further 11 children had been lost to follow up during the previous six years. During January 78 sets of questionnaires were sent out In March non-specific bronchial provocation testing and skin tests for atopy were performed on as many parents and children who responded to the questionnaire as possible.

Control subjects. These were taken from a recent survey of Southampton schoolchildren using the same respiratory questionnaire and included 1276 children aged between 6·8 and 7·8 years (mean age 7·3 years).[15] Of these, 157 selected from different symptom groups were later successfully tested for bronchial response to methacholine and atopy as in the cohort survey Prevalence figures for atopy and bronchial responsiveness to methacholine were derived by extrapolation from each symptom group tested to the frequency in the general population.

Questionnaires.[†] Parents were asked to complete two questionnaires, one concerning symptoms in the index child and the other in the patient with asthma The three questions used to indicate wheeze, dyspnoea, and cough were 'Has your child ever had attacks of wheezing (by wheezing I mean noisy breathing with a whistling quality coming from the chest not the throat)?'; 'Has your child ever been unexpectedly breathless or more breathless than you would expect after exercise (by breathless I mean out of breath or puffed)?', and 'Has your child ever seemed to cough more than other children?'. Some parents answered positively only to the questions enquiring about night or morning cough and these children were also designated as having cough. Detailed information was sought on each symptom, including whether it had occurred in the preceding 12 months, in which case the symptom was coded as 'current'. Further questions were added concerning the existence of hay fever or eczema ('eczema or patches of dry, itchy skin').

The parent's questionnaire was shorter and sought confirmation of diagnosis of asthma in addition to information on severity and provoking factors The three historical questions used to indicate bronchial irritability in the parents were those shown by Mortagy *et al* as predictive of bronchial hyper-responsiveness in Southampton adults:[16] 'Do you ever wake up at night with breathlessness?'; 'When you get up in the morning how does your chest feel: free or tight; if tight how long does it take to become free?'; and 'Do any of the following give you either shortness of breath or wheezing: going from a warm room into a cold room; entering a room where people are smoking; traffic fumes; chemicals—for example, hair spray, bleach, perfumes?'

Both questionnaires provided for information on current medication.

Measurement of bronchial responsiveness. The method used was that described by Yan *et al*[17] and recommended by Woolcock[18] for epidemiological work. This method was chosen for its simplicity and speed Methacholine was chosen as the provoking agent because of the absence of side effects, stability in solution, and economy; on a molar basis its potency as a bronchoconstrictor agent is reputed to be similar to histamine.[18]

The methacholine aerosol was delivered from hand held DeVilbis number 40 glass nebulisers The output of each nebuliser was measured by weighing before and after the same operator squeezed the bulb 10 times on 10 separate occasions. Five nebulisers were chosen with output coefficients of variation of less than 15% Concentrations were adjusted according to nebuliser output and required dose.

After instruction in the use of a dry wedge bellows spirometer (Vitalograph Ltd, Buckingham, England) the subject's baseline forced expiratory volume in one second (FEV$_1$) and forced vital capacity were measured and the highest reproducible value recorded. The bulb of the nebuliser was then squeezed by the operator at the beginning of an inspiration from functional residual capacity to total lung capacity and the subject asked to breath hold for three seconds. After 60 seconds FEV$_1$ was measured and the higher value of two measurements that were reproducible within 0·2 litres in adults and 0·1 litres in children was recorded. After an initial inhalation of normal saline subjects were given increasing doses of methacholine from 0·025 µmol to 6·4 µmol. This is equivalent to a concentration range of 0·08 mg/ml to 20 mg/ml using the methodology of Cockcroft *et al*.[5] [19] Doubling doses were administered to severe or labile adults with asthma and in all children with symptoms of asthma. In the remaining subjects quadrupling doses were used unless a 10% fall in FEV_1 was recorded, in which case they were moved to the slower regimen. The dose given was expressed cumulatively by including previous doses

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[†] Copies of the questionnaire used can be obtained on application to Dr R Clifford, Medicine 1, Southampton General Hospital, Tremona Road, Southampton

The test was continued until either the highest dose had been administered or a greater than 20% drop in FEV_1 from the post-saline measurement had been recorded, in which case the result was scored 'positive'. Any bronchoconstriction caused by the methacholine was then reversed with inhaled salbutamol. The cumulative provocation dose of methacholine required to cause a 20% fall in FEV_1 (PD_{20} methacholine) was calculated from a log dose response curve by linear interpolation.[18]

Skin testing. Saline and histamine controls together with three allergen extracts—*Dermatophagoides pteronyssimus*, mixed grass pollens, and cat dander (Bencard, Middlesex)—were used for intradermal testing. The skin was pricked through the solution on the anterior aspect of the forearm, using a sterile 25 gauge needle, without drawing blood Any weals produced by the control solutions of allergen extracts were measured after 10 minutes and the diameters recorded. Those with diameters greater than 3 mm were scored positive.

Data analysis. Data was coded and stored on an ICL2976 computer. Analyses were performed using the statistical package for social sciences.[20] χ^2 Tests using Yates's correction were used to assess the significance of differences in proportion of symptoms between the cohort and the general population. Fisher's exact test was used to measure the association between atopy and bronchial responsiveness. Where appropriate, 95% confidence intervals for the difference between proportions have been supplied as recommended by Gardner and Altman.[21]

Results

Responses. Of the 78 sets of questionnaires posted, 50 were returned completed and 16 were returned with the response 'moved, address unknown', giving a return rate of 81% (50/62). The mean age of the children was 6·4 years. Of the 50 respondents, 35 agreed to attend with their children for skin testing and measurement of bronchial response to methacholine Three failed to keep their appointment Thus 32 parents and 32 children were seen for testing. Four parents and three children were excluded from methacholine provocation testing either because their baseline FEV_1 was less than 70% predicted (two parents and two children) or because the subject was unable to perform the procedure (two parents and one child). All 64 parents and children attending the department were skin tested.

Parent's questionnaire. Information was not available on one parent who had died since collection of the cohort Table 1 shows data on severity of asthma together with the symptoms of bronchial irritability. Thirty nine (81%) of 48 parents were receiving medication for asthma but only 25 (51%) had seen their doctor in the previous 12 months. Forty five (92%) parents answered positively to one or more of the three symptom questions, with 44 of these experiencing the symptom of wheeze or dyspnoea precipitated by exposure to cold air, chemicals, fumes, or smoke.

Children's questionnaire. Ten children (20%) had

Table 1 *Morbidity (%) due to asthma and symptoms of bronchial irritability in the 49 parents*

Receiving asthma medication	81
Visited doctor for asthma in previous 12 months	51
Hospital admission in previous 10 years	12
More than five days off work in previous 12 months	20
Morning tightness >1 hour	20
Nocturnal dyspnoea	71
Wheeze or dyspnoea with cold air, chemicals, fumes, or smoke	90

Table 2 *Prevalence of symptoms in a cohort of 50 children (mean age 6·4 years) with one parent with asthma compared with 1276 children from a general population sample (mean age 7·3 years)*

Symptoms	*Current prevalence (%)*		*Cumulative prevalence (%)*	
	Cohort	*Control*	*Cohort*	*Control*
Wheeze	22	11·9	28	19·4
Shortness of breath	16*	6·9	16	9·8
Cough	62**	32·5	66**	43·7
Eczema	NA	NA	40	NA
Hay fever	NA	NA	24	NA
Morning symptoms	40**	22·7	40	28
Nocturnal symptoms	48***	22·4	52*	34
Symptoms induced by exercise	34	35·7	NA	NA

*$p<0·05$ **$p<0·01$, ***$p<0·001$, by χ^2 test with Yates's correction
NA=Not assessed

been given a diagnosis of asthma by their general practitioner. Current and cumulative prevalences of symptoms of asthma together with eczema and hay fever are displayed in Table 2 and compared with data from the Southampton general population survey. All prevalence figures for respiratory symptoms, both current and cumulative, were one and a half to two times greater in the cohort children except for symptoms produced by exercise, chemicals, fumes, or smoke. The difference in prevalence of wheeze just failed to reach significance at the 5% level. The 95% confidence interval for the difference between the prevalence of wheeze in the cohort and the prevalence of wheeze in the general population=+24·4% to −4·2%. The prevalences of eczema, 40%, and hay fever, 24%, were also high in the cohort.

The prevalence of symptoms in response to such provoking agents as chemicals, fumes, smoke, cold air, or exercise was similar between the cohort and the general population (Table 2). No child in the cohort group, however, had symptoms only in response to these provoking stimuli, which compares with 20% in the general population. Thirty three (66%) of the 50 children had experienced breathlessness, wheeze, or problematic cough during the preceding 12 months, which compares with an expected figure of 18 subjects. Cough as the only symptom occurred with twice the prevalence in the cohort compared with the general population.

Respiratory function tests. Of 32 adults and children attending for testing, the FEV_1 was satisfactorily recorded in 31 adults and 30 children (Fig. 1). PD_{20} for methacholine was measured in 28 adults and 29 children (Fig. 2). The mean per cent predicted FEV_1 in the parent group was 92% and in the children 113%. No parent or child with a FEV_1 below 75% expected underwent methacholine provocation. Twenty six (93%) parents were found to have a PD_{20} of <6·4 µmol. Thirteen (45%) children had a PD_{20} of <6·4 µmol, which compares with 29·4% in

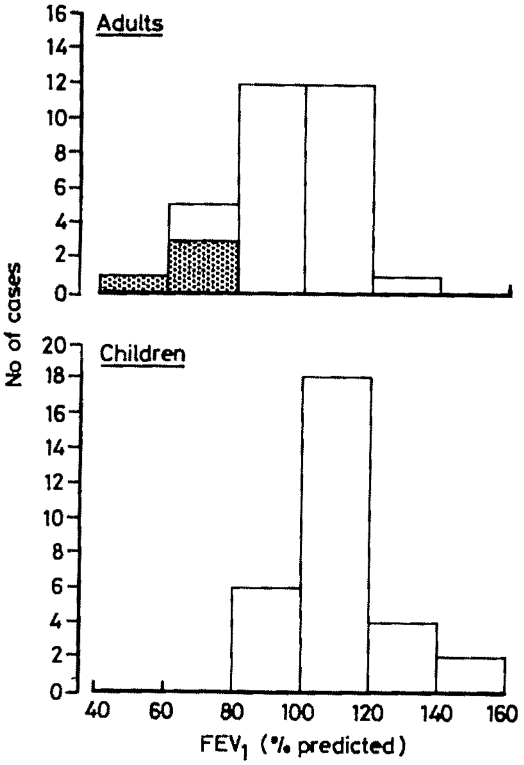

Fig. 1 *Distribution of measurements of forced expiratory volume in one second (FEV_1) in adults with asthma compared with their children Shaded area represents subjects not tested for response to methacholine as FEV_1<75% predicted*

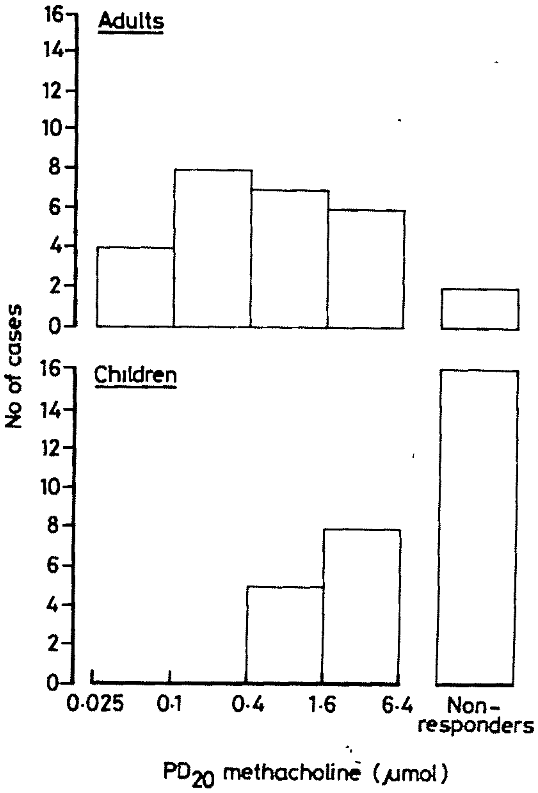

Fig 2 *Distribution of cumulative provocation dose of methacholine to cause a 20% fall in forced expiratory volume in one second (PD_{20} methacholine) among adults with asthma and their children*

general population at 7 years calculated from the schools survey. This difference did not reach significance. The 95% confidence interval was calculated as: proportion in cohort responding to <6·4 µmol methacholine-proportion in general population responding to <6·4 µmol methacholine=+34·9% to −4%. The distribution of responsiveness was broader in the adults than in the children and no child had a PD_{20} of less than 0·4 µmol compared with 12 adults (43%) (Fig. 2).

Skin tests. The results of the skin prick allergen tests are displayed in the form of a Venn diagram in Figure 3. All 32 adults and children were successfully tested. Twenty eight (88%) parents were atopic (one or more positive skin tests). Just six (19%) children in the cohort, however, were shown to be atopic compared with an expected prevalence of 24·5% at 7 years calculated from the schools survey. The 95% confidence limits for the difference was: prevalence of atopy in the cohort-prevalence of atopy in general population =+9·8% to −20·8%. Hence there was only a 0·025 probability of a 10% or greater increased prevalence of atopy in children with one parent with asthma at this age. Ten parents but no children were positive to all three allergens. There were no cases in either the children or the parents where cat dander was the only positive test.

Relations between symptoms and objective testing. The combined data from the symptom questionnaire, skin allergen tests, and methacholine bronchial provocation are displayed in the form of a Venn diagram in Figure 4. For the purposes of this diagram a child who had any of the current respiratory symptoms listed in Table 2 has been classed as symptomatic. Parents have been classed as symptomatic if they had any of the current symptoms of bronchial irritability listed in Table 1.

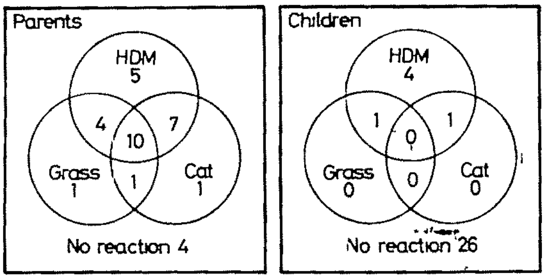

Fig 3 *Venn diagram representing the results of skin prick testing to house dust mite (HDM), mixed grass pollen (Grass), and cat fur (Cat) allergen extracts in adults with asthma and their children*

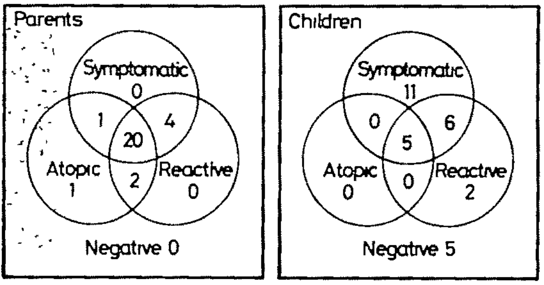

Fig 4 *Relation between symptoms, atopy, and bronchial responsiveness to methacholine (reactive) in adults with asthma and their children*

All symptoms were current Twenty five of 28 parents tested for bronchial responsiveness to methacholine and atopy answered positively to these questions, and of these, 24 (96%) responded to methacholine. Two parents who denied symptoms of bronchial irritability and who were both atopic responded to methacholine. In the children no significant association was found between any one respiratory symptom, or combination of symptoms, and methacholine bronchial responsiveness. Of 16 children who failed to respond to any dose of methacholine, 11 had one or more of the symptoms listed in Table 2, including wheeze or shortness of breath (five cases). Two children who had none of these symptoms were responsive to methacholine, although in both cases this was to the last dose given (6·4 µmol).

In the children there was a significant relation between methacholine bronchial responsiveness and atopy (p=0·002, Fisher's exact test). Five of six atopic children had bronchial provocation tests. All five were responsive to methacholine and had symptoms. A further six children who had symptoms and a positive methacholine provocation test were not atopic None of the 11 symptomatic children who failed to respond to methacholine were atopic. The two asymptomatic children, who were responsive to methacholine, were both atopic. The remaining five children were unresponsive to methacholine, not atopic, and asymptomatic.

Discussion

Symptom quesionnaire. This study showed higher prevalences of respiratory symptoms in a cohort of children with one parent with asthma than in the general population survey of children of similar age conducted in Southampton during the same 12 months The current prevalences of wheeze (22%), shortness of breath (16%), and cough (62%) were all about double that in the general population. Using similar questions, the child health and education survey has shown overall prevalences of 12·2% and 4·2% for reported eczema and hay fever using a health visitor administered questionnaire.[22] We have shown threefold and sixfold prevalences of these complaints in our cohort. This shows a considerable increase in the occurrence of allergic illness in children who have one parent with asthma.

Asthma has a high prevalence in adults and children. The general population data inevitably included many children with a family history of asthma Thus exclusion of such children from these control data would have further increased the differences shown in this study. The mean age of the cohort (6·4 years) and the children in the schools survey (7·4 years) was slightly different, raising the possibility that some of the differences may have been age related. In the schools study we showed that the prevalences of wheeze and shortness of breath were similar at 7 and 11 years but that a fall in the prevalence of cough from 32·5% to 21% occurred.[15] In view of the differences in only some symptoms during the four year interval between 7 years and 11 years, however, it seems unlikely that a one year interval would have significantly altered these data.

Bronchial response to methacholine. In the cohort 45% of children responded to a dose of 6·4 μmol or less of methacholine compared with an expected figure of 28·9% from the schools survey Although this difference just failed to reach significance at the 5% level, the 95% confidence intervals show that this result is consistent with a large increase in methacholine responsiveness between the cohort and general population in line with the higher prevalences of respiratory symptoms.

Atopy. In the present cohort of children aged between 5·3 and 7·3 years the prevalence of positivity to one or more of the three allergens tested was 19%. The difference between this and the calculated population prevalence of 25·5% is surprising but not significant. Calculation of the 95% confidence intervals shows that a >10% increase in the prevalence of atopy in this age group in children with one parent with asthma is unlikely None of the 34 parents and children found to be atopic among our subjects was negative to both house dust mite and grass pollen. Thus the use of the cat dander extract failed to identify any further atopic subjects

Relations between symptoms, atopy, and bronchial responsiveness. In this cohort all five children who were both symptomatic and atopic responded to doses of less than 6·4 μmol methacholine. Two thirds of the non-atopic children failed to respond, although a high proportion (69%) had symptoms suggestive of asthma (Fig. 4). In this latter group increased responsiveness of the airways may only become manifest after a viral upper respiratory tract infection.[23] Gregg has suggested that the age related improvement in respiratory symptoms in many children with wheezing induced by viral infections may occur as a result of spontaneous improvement in specific lower respiratory tract defence mechanisms together with acquisition of immunity to a progressively greater number of respiratory viruses.[24] If atopy should later develop continued exposure to at least one allergen such as house dust mite faecal antigens could provide a persistent stimulus, resulting in the acquisition of a more permanent state of non-specific bronchial responsiveness detectable on formal testing. Platts-Mills has shown that enhanced bronchial responsiveness associated with symptoms of asthma may decrease substantially in a controlled dust free environment.[11] Apart from such artificial situations, however, dust mite allergy results in almost inevitable daily allergen challenge. Thus we are able to propose a model that might explain the relation between classical asthma and 'wheezy bronchitis', a diagnosis over which there is much confusion The consistent presence of methacholine bronchial responsivenes in the atopic children in our cohort compared with its absence in 11 of 17 symptomatic children who were not atopic is further support for this suggestion.

Whereas we have shown high prevalences of symptoms in this cohort, many of these children experienced cough as their only symptom. Out of cough, wheeze, and shortness of breath, only wheeze showed a non-significant increase from the general population prevalence ($0·05<p<0·1$), while cough was highly significant ($p<0·01$). Many of these children suffered from nocturnal cough, which overall was the most common cause of nocturnal symptoms The increased prevalence of nocturnal symptoms in the cohort was again highly significant ($p<0·001$)

The greater prevalence of cough alone compared with the general population suggests a specific disease· one fifth of schoolchildren with no other respiratory symptoms are considered by their parents, however, to have problematic cough (Table 3). Nevertheless, cough as the single presenting feature of asthma is now a well recognised occurrence. Many children with intermittent symptoms of asthma triggered by viral upper respiratory tract infections do not wheeze as their major symptom

Table 3 *Distribution of 50 children in the cohort among seven symptom groups compared with 1162 children from a general population sample*

Symptom classification	*Cohort (%)*	*Control (%)*
No current symptoms or past wheeze/ shortness of breath	34	43
Cough alone	40*	20·7
Wheeze and/or cough	10	7·2
Shortness of breath and/or cough	4	1·9
Wheeze and shortness of breath and/or cough	12	5·7
Symptoms only induced by exercise, fumes, smoke, or cold air	0**	20·0
Wheeze/shortness of breath in the past, no current symptoms	0	1·5

*$p<0·01$, **$p<0·001$, by χ^2 test with Yates's correction

but are more troubled by cough, particularly at night. In such children serial peak flow recordings, tests of reversibility of airways obstruction, and non-specific bronchial provocation may all be useful investigations before a trial of treatment is attempted; these procedures are still unavailable, however, in the absence of sophisticated equipment for very young children. Moreover, recent evidence suggests that such investigations are fallible as many children with clear symptoms of asthma do not show bronchial responsiveness to methacholine.[2]

In our general population study we have shown that these non-responders are mainly confined to the non-atopic group. Ninety three per cent of atopic children with wheeze respond to methacholine against just 17% of non-atopic children. Despite the high prevalence of symptoms of asthma in the cohort, we were unable to show a significant difference in the prevalence of methacholine responsiveness compared with the general population. This is partly due to the small number of atopic children among those tested. The increased tendency to allergic illness in these children is shown by the high prevalences of eczema and hay fever, suggesting that skin and pulmonary sensitivity to inhaled allergens may develop at a later date. A future study of the prevalence of bronchial responsiveness to methacholine in this cohort when the children are older would be interesting and may yield different results.

In conclusion, this study has shown that children with one parent with asthma, when compared with a recent general population study in schoolchildren, have roughly twofold prevalences of wheeze, shortness of breath, and cough with one and half times the prevalence of non-specific bronchial hyperresponsiveness of objective measurement. High prevalences of eczema and hay fever but not atopy were also shown. We were able to establish a close relation between non-specific bronchial hyperresponsiveness and the presence of atopy, suggesting a causal interaction.

We thank Mr F Anderson for performing all the bronchial provocation tests on the adult subjects and Dr M Campbell for statistical advice

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Short reports

Preterm blood counts vary with sampling site

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SUMMARY In preterm babies both haemoglobin and total neutrophil count values from capillary sites are significantly and variably higher than those from simultaneous arterial samples Comparing simultaneous venous and arterial samples, the mean haemoglobin was slightly higher but the total neutrophil counts were similar.

Recent improvements in neonatal intensive care have resulted in an increasing number of small, very sick infants being cared for in specialised units. They are usually intensively monitored and investigated. Blood counts are performed very frequently, often daily, on ill babies. Sampling may be by direct arterial puncture, from an umbilical vessel catheter (arterial or venous), a peripheral vein, or a heel prick (capillary). The results are used for estimating the volume of blood required for transfusion (haemoglobin) or for assessing the possibility of infection (neutrophil count).[1] In term babies the method of sampling has been shown to affect the blood count results.[2] This report shows the same effect in preterm infants.

Methods

A preliminary survey was carried out to determine blood sampling methods in units offering neonatal intensive care in London. At St George's Hospital neonatal unit samples were taken in the first week of life from infants of 24 to 32 weeks' gestation, with a mean (SD) birth weight of 1211 (311) g, who were being ventilated for respiratory distress syndrome and who had umbilical arterial catheters (UAC) in situ. First, 0·5 ml of blood from the UAC was placed in tubes containing edetic acid. Then a further 0·5 ml was obtained by freeflowing heel prick (n=13) or by peripheral venepuncture from the back of the hand (n=21). Sampling coincided with Detrostix measurement to avoid unnecessary trauma to the babies. Blood counts were performed on a Coulter S+4 counter and the differential white blood cell count was determined by examining the slides 'blind' in batches at a later date.

Two tailed paired *t* tests were used to compare the results between pairs of samples.

Results

Table 1 shows the different ways in which blood count samples are taken in various units in London. If an arterial line is in situ most senior house officers use this for taking blood for blood counts. Otherwise the units are evenly divided about whether samples are taken from heel pricks or by peripheral venepuncture

Table 1 *Survey of methods of taking blood for blood counts in 12 neonatal intensive care units in London*

Unit No	*Sampling method*		
	Arterial	*Venous*	*Capillary/heel prick*
1	UAC if available	Usually	Rarely
2	Usually UAC or direct arterial puncture	Only if no blood gas needed	Very rarely
3	Occasionally (UAC)	Rarely	Most times
4	UAC if available	Normally	Occasional only
5	UAC/radial line if available	Sometimes	Usually
6	Arterial line if available	Sometimes	Quite often—especially if only haemoglobin wanted
7	Arterial line if available	Occasionally—if also doing coagulation, etc	Usually
8	Arterial line if available	Occasionally only	If no arterial line, usually
9	If doing gas/line up	If not doing gas	Last resort only
10	UAC if available	Usually	Last resort
11	Arterial line if available	Usually	Rarely
12	Arterial line if available	If not doing blood gas	Rarely

UAC=Umbilical arterial catheter

Table 2 *Haemoglobin and neutrophil count results according to method of sampling*

Method of sampling	*(n=)*	*Haematological measurement (mean (SD))*	
		Haemoglobin (g/dl)	*Neutrophils ($\times 10^9$/l)*
Arterial	13	14·1 (2·1)	3·7 (1·5)
Capillary		16·4 (2·9)	5·5 (3·0)
p Value*		<0·001	<0·01
Arterial	21	13·3 (3·0)	9·8 (7·9)
Venous		13·8 (3·0)	10·4 (8·0)
p Value*		<0·001	NS

*By paired *t* test
NS=Not significant

Table 2 illustrates the differences in blood count results using the different methods. The difference between capillary (heel prick) and arterial samples are most pronounced. Every capillary haemoglobin value was higher than its corresponding arterial sample ($p<0{\cdot}001$), with a mean difference of 2·3 g/dl (range 0·6–4·9 g/dl). Similarly, the capillary neutrophil count was higher than the arterial in each sample pair by an average difference of $1{\cdot}8\times10^9$/l ($p<0{\cdot}01$) (range $0{\cdot}4$–$5{\cdot}9\times10^9$/l). There were also differences of a lesser degree between venous and arterial samples. The haemoglobin was higher in the venous samples ($p<0{\cdot}001$). The mean difference was 0·5 g/dl, and only one arterial value was higher than the venous in 21 pairs. Although the mean neutrophil count was higher in the venous than the arterial samples, 10·4 *v* $9{\cdot}8\times10^9$/l, the difference was not significant There were no significant differences in the platelet counts or other types of white cells using the different collecting methods (data not shown).

Discussion

Haematological values are important for making clinical decisions in the neonatal unit. An infant with hypovolaemia may receive a colloid solution rather than blood for volume support if the haemoglobin value is high The haemoglobin value is used as a basis for calculating the amount of blood needed for a top up transfusion. The number of neutrophils may be used as supporting evidence for infection[1] and the need to start or change antibiotics or perform an infection screen. The data presented here show that haematological values vary markedly according to the sampling method.

If we start from the assumption that the central arterial values are the most reliable and representative the magnitude and variability of the difference of the haemoglobin of capillary specimens compared with arterial ones is clinically important, for instance influencing adversely the decision regarding the volume of blood necessary to be transfused. The venous samples, though statistically higher than arterial ones ($p<0{\cdot}001$), are not such a problem, firstly because the difference is not so great and secondly because it is consistent in magnitude, never being more than 1·4 g/dl. Presumably the difference is related to the passage of plasma to the interstitial compartment in the capillary bed, which is returned to the circulation through the lymphatic channels.

Similar problems are seen on considering total neutrophil count. The average difference of capillary compared with arterial neutrophil count was $+1{\cdot}8\times10^9$/l and on one occasion was twice as high from the capillary site. If, after the removal of the arterial catheter, capillary sampling was relied on this might increase the likelihood of an invasive infection screen and an antibiotic course. The venous and arterial difference in neutrophil count was not significant so venous sampling should give reliable results

The published reports vary concerning the reference ranges of haematological values in preterm infants. This may be partly due to the site of sampling Lloyd and Oto used only capillary sampling.[3] Manroe used a mixture of methods.[4] This may lead to arterial or venous samples being regarded as 'neutropenic' when matched against a capillary reference range. We feel that it is important both to sample from a venous or arterial site and to use a reference range applicable to both this site and these small and immature infants.

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Chloroquine treatment in desquamative interstitial pneumonia

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SUMMARY An infant presented with failure to thrive, tachypnoea, and hypoxia reversed by oxygen. Lung function showed decreased pulmonary compliance; lung biopsy showed desquamative interstitial pneumonitis. Chloroquine 10 mg/kg/day resulted in improvement and relapse when temporarily stopped. The patient was completely asymptomatic during four years' treatment and six months after stopping treatment.

Desquamative interstitial pneumonia is uncommon in infancy, and although the histological features resemble those of adults, the clinical presentation and response to treatment tend to differ. Infants have a rapidly progressive disease characterised by tachypnoea, dyspnoea, cough, cyanosis reversed by oxygen, and hyperinflation of the lungs.[1] Although spontaneous remissions have been reported,[2] it is usually a fatal disease unless treated. The usually accepted treatment is with corticosteroids or a combination of corticosteroids and cytotoxic drugs. Even when treated, the mortality in infancy can be up to 50–60%.

An alternative approach to treatment was reported by Tooley, who obtained a good response to treatment with chloroquine in a girl with desquamative interstitial pneumonia.[3]

We present a report of an infant with severe desquamative interstitial pneumonia in which we obtained objective evidence of a dramatic response to chloroquine.

Case report

A 4 month old boy was admitted because of anorexia and poor weight gain from the age of 2 months. He was born after a normal pregnancy, weighing 3150 g, and the history was otherwise unremarkable. An older sibling had been admitted with a similar problem of failure to thrive, which was eventually diagnosed as a psychosocial problem and successfully treated.

Physical examination on admission revealed a 4·8 kg infant with mild tachypnoea and a temperature of 37·5°C. No other physical abnormalities were noticed. Chest *x* ray film showed moderate bilateral hyperinflation. Arterial blood gases breathing room air showed pH 7·39, oxygen tension 7·1 kPa (53 mm Hg), and carbon dioxide tension 4·5 kPa (34 mm Hg).

In the first two months of admission to hospital the main problems were failure to thrive, anorexia, and mild tachypnoea. Cystic fibrosis, immunodeficiency, malabsorption, and renal and metabolic abnormalities were excluded and it was (erroneously) thought that his problem was similar to that of his older brother. In the third month after admission the patient became more tachypnoeic and a repeated arterial blood gas analysis in room air showed oxygen tension 5·1 kPa and carbon dioxide tension 5·5 kPa. When given oxygen his oxygen tension rose to 39·3 kPa, suggesting ventilation-perfusion imbalance.

Pulmonary function tests were performed using the infant whole body plethysmograph.[4] Thoracic gas volume and specific airway conductance were normal (150 ml and 4·1 sec/kPa), whereas specific dynamic compliance was 0·296 kPa (normal=0·60 kPa). Measurement of forced expiratory flow[5] revealed normal flow at resting lung volume (280 ml/sec). At 7 months an open lung biopsy examination was performed. Histological findings were mild thickening of the alveolar septa, and groups of desquamated type II pneumocytes and macrophages within the alveolar spaces, which were identified on electron microscopy studies. The picture was typical of desquamative interstitial pneumonia. Stains and cultures of the biopsy specimen for pneumocystis, bacteria, fungi, and acid fast organisms yielded negative results.

The patient was treated with chloroquine 10 mg/kg in two divided doses. After one month of treatment he started to improve and his respiratory symptoms subsided, and after two months of treatment no supplemental oxygen was needed. Arterial oxygen tension in room air rose to 8·9 kPa and he started to gain weight. After six months of treatment chloroquine was stopped for three weeks, at the end of which his arterial oxygen tension had fallen to 5·7 kPa. Chloroquine was restarted and his oxygen tension rose again (Figure). After 16 months of treatment his weight reached the 3rd centile and after another year the 25th centile. Repeated arterial blood gas examinations yielded normal results. Ophthalmologic examinations were performed every six months and yielded complete

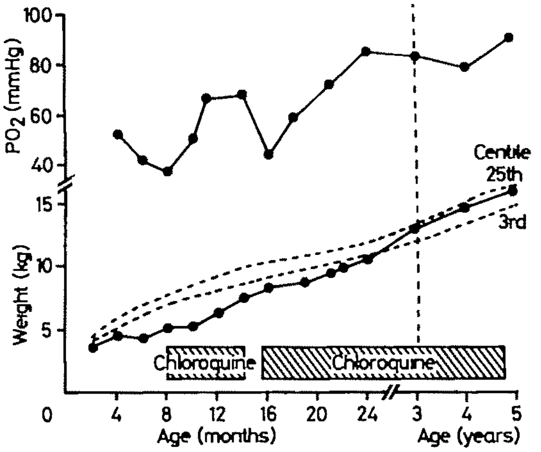

Figure *Weight and arterial oxygen tension (PO$_2$) before and during treatment with chloroquine*

results. At the age of 4·5 years chloroquine was stopped. Six months later arterial oxygen tension was 12 kPa and chest *x* ray film and a xenon perfusion lung scan yielded normal results.

Discussion

Although spontaneous resolution of desquamative interstitial pneumonia may occur occasionally,[2] there is little doubt that our patient responded to chloroquine, as stopping of the treatment resulted in deterioration of his condition and restarting the treatment brought about a second improvement. This response is similar to that originally noted by Tooley.[3] Leahy *et al* reported an infant who was unresponsive to chloroquine alone but who responded to a combination of chloroquine and steroids initially and to chloroquine alone later.[6]

Although hyperinflation was evident on the chest radiograph, lung function revealed a normal thoracic gas volume more in keeping with the physiological pattern seen in adults.

Antimalarial compounds have been shown to inhibit in vitro antigen antibody complex formation and to split immune complexes. Raised concentrations of circulating immune complexes and deposition of immunoglobulin and complement in the lungs have been shown in patients suffering from idiopathic interstitial pneumonia. These findings suggest that antimalarial agents may be effective in the treatment of desquamative interstitial pneumonia through an immunosupressive mechanism.

Chloroquine is not an entirely harmless drug The most serious complication is retinopathy, which is probably a dose related phenomenon. The alternative to chloroquine is treatment with steroids or cytotoxics, or both, which, apart from the variable response, also have side effects.

We suggest that chloroquine should be considered as an effective alternative treatment in desquamative interstitial pneumonia. Careful observation is needed to evaluate its efficacy and safety in children.

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Congenital isolated folic acid malabsorption

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SUMMARY We report a case of congenital isolated malabsorption of folic acid, the first in a boy. Only seven previous cases have been reported, and we discuss two aspects—namely, the tendency to infection, with evidence of impairment of both cellular and humoral immunity, and the absence of neurological disturbances.

Congenital isolated malabsorption of folate is a rare and specific disorder, causing megaloblastic anaemia in early childhood, which can be corrected by administering very high doses of folic acid orally or by parenteral administration of physiological doses. The case reported here is the first in a boy.

Two additional aspects will be emphasised: our patient (a) showed no neurologic disturbances and (b) suffered from a tendency to infections apparently due to partial immunodeficiency.

Case report

A five month old Moslem boy was admitted to hospital with recurrent infections, severe anaemia, and failure to thrive. He was the seventh child of healthy parents, who were first cousins. Two of their seven children had died during the first year of life without definite diagnosis.

The patient was born after a full term pregnancy with a weight of 3500 g. He was breast fed for one month only and then fed on SMA formula From the fourth month of life the child began to suffer from recurrent infections, especially of the upper respiratory tract, lungs, ears, and gastrointestinal tract. On admission his general condition was very poor; he was very pale and feverish (38·2°C) He showed failure to thrive in both weight (5050 g) and height (59 cm). Bilateral otitis media and bronchopneumonia were present. On first admission, the haemoglobin was 9·0 g/dl, packed cell volume 27%, and white blood cell count 12 800/mm^3, with normal differential count and mild thrombocytopenia of 100 000/mm^3 Tests on urine and all other biochemical tests yielded normal results.

The most striking clinical disturbance was severe and chronic anaemia during the fifth and sixth months of life, with haemoglobin concentrations ranging from 4·5 to 9·2 g/dl and packed cell volume between 15% and 29% and with mean corpuscular volume of 100 u^3. The peripheral blood smears showed macrocytosis and hypersegmentation of polymorphonuclear cells; the leucocyte count was in the range of 7000–12 000 mm^3 and thrombocytes 100 000–200 000/mm^3, with reticulocytes 0·2–1·0%. Coombs tests yielded negative results, and both a Motulsky test and electrophoresis of haemoglobin showed normal results. These data together with the macrocytosis found in the peripheral blood smear were compatible with a diagnosis of megaloblastic anaemia, which was confirmed by the findings of megaloblastic changes in the bone marrow.

The megaloblastic anaemia was found to be due to folic acid deficiency, as indicated by the low concentrations of folic acid in red blood cells (15–50 ng/ml, while the normal value is above 250 ng/ml), serum (<1 ng/ml, while normal is above 5 ng/ml), and cerebrospinal fluid (<1 ng/ml, while normal is 15 ng/ml), Blood concentrations of vitamin B_{12} were 700–800 pg/ml and urine orotic acid concentration was normal too. The folates were determined by the microbiologic assay of Grossowicz *et al*,[1] using *Lactobacillus casei* as test organism. The diet of the mother during lactation and the child's diet were found to be normal, the possibility of dietary folate

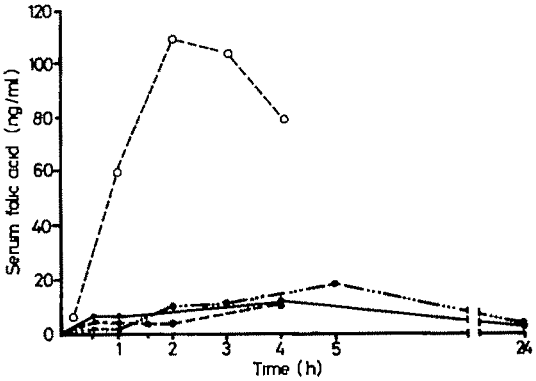

Figure *Oral folic acid loading tests, assayed with* Lactobacillus casei,[1] *in the patient aged 9·5 months (● – – – ● = 5 mg folic acid; ●——● = 10 mg folic acid; ●–· –● = 10 mg folinic acid) and in a control aged 9 months (○ – – – ○ = 5 mg folic acid)*

Table *Concentrations of serum folate before and after treatment with folic acid*

Body fluids	*Before treatment (ng/ml)*	*After oral administration (ng/ml)*	*After intravenous administration (ng/ml)*
Serum	<1 0	<1 0	1 7
Whole blood	30–50	20–90	420
Cerebrospinal fluid	1 0	1 0	4 0

deficiency was thus excluded. The diagnosis of malabsorption of folate was confirmed by the unchanged concentrations of serum and red blood cell folate after oral loading tests of 5 mg and 10 mg folic acid, respectively, as well as of 10 mg folinic acid (5-formyltetrahydrofolate), as shown in the Figure, and by reaching normal concentrations of red blood cell folate after intravenous administration of 5 mg folic acid (Table). Treatment consisted of three consecutive daily doses of 5 mg each of folic acid given intravenously and then observation for three weeks before being discharged in good condition.

A gastrointestinal evaluation made to reveal other defects of absorption in the intestine gave normal results in loading tests of glucose and fat. The sweat test yielded normal results as did tests of the pancreatic enzymes lipase, amylase, and trypsin in the duodenal juice. Small intestine biopsy examination revealed normal mucosa; *Giardia lamblia* was not found. The diagnosis of isolated malabsorption of folic acid was thus established.

In connection with the recurrent infection an immunological evaluation was performed; normal concentrations of IgG (1002 mg/100 ml) and a fairly high concentration of IgM (326 mg/100 ml) were found. IgA was undetectable. Of the family members tested (parents and three siblings), all showed normal concentrations of immunoglobulins. On the other hand, cellular immunity was decreased in both T cells (E rosettes forming and response to phytohaemagglutinin and concanavalin A) and B cells (surface Ig and response to pokeweed mitogen). C_3 complement concentration was normal (184 mg/100 ml) and immune complexes were not found

The failure to thrive that was seen in the infant on first admission continued during the three consecutive admissions to hospital. These failures could be explained, in part at least, by the anaemia and recurrent infections, which became milder after the age of 6 months when the child's general condition improved considerably. Because of this improvement, his parents, who were not particularly cooperative, refrained from bringing the child to hospital unless his condition worsened considerably. No psychomotor retardation was observed in the child. On the last admission, at the age of 14 months, the child arrived in a very neglected condition and with severe anaemia. He immediately received a blood transfusion but died unexpectedly of severe bilateral pneumonia, which did not respond to aggressive antibiotics and other treatment, before a regular course of treatment with parenteral folic acid could be established

Discussion

Congenital malabsorption of folic acid is a rare and specific defect of the absorption of this vitamin from the gastrointestinal tract in the absence of malabsorption of any other nutrient.[2] It has been shown, in the few cases described by others, that the defect persisted after considerable doses of folate were given orally.[2–4] This was also the case with our patient, who responded only to parenteral folate. All seven cases described in the published reports were girls; recently, an X linked defect was hypothesised.[5] Our case in a boy supports the possibility of autosomal or multifactorial inheritance.

In contrast to the cases described by others,[2–4] ours is unique in that there were no signs of mental retardation or any convulsive disorders. Correction of serum folate concentrations was accompanied by correction of cerebrospinal fluid folate concentrations to the normal serum:cerebrospinal fluid ratio of 1:3, which indicates that no transport defect of folate through the blood-brain barrier occurred.

The immunological work performed because of the recurrent infections revealed partial deficiency in both humoral and cellular immunity. The findings of decreased T cell function in folate deficiency were reported even though increased tendency to develop infections was not present.[5] Corbeel *et al* described a case showing a tendency to infections.[6] The only immune deficiency found by them, however, was a low concentration of immunoglobulins Whether a correlation between folate deficiency and a tendency to recurrent infections is a common finding cannot be answered before a follow up of more cases of this rare disorder is undertaken. This also holds true regarding the question of whether there is more than one type of congenital folate malabsorption.

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Tachycardia and heart failure after ritual circumcision

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SUMMARY Four newborn babies developed acute heart failure a few hours after circumcision at 8 days. During this procedure, a sponge soaked in epinephrine was applied to the circumcision site and left there for several hours. Treatment was with digoxin and diuretics and signs of heart failure disappeared within 24–72 hours.

Circumcision is the operation most often performed on males in Israel and the United States.

We describe a complication of this procedure that has not hitherto received publicity.

Case reports

The four babies described here were admitted to the paediatric intensive care unit a few hours after ritual circumcision, which was performed at 8 days of age. All were born normally at term after normal pregnancies, and there were no postnatal complications.

On admission the clinical signs in each baby were similar, consisting of pallor, central cyanosis, tachycardia, tachypnoea, and grunting respirations (Table)

Their heart rates were over 200 beats per minute and the liver was enlarged in three patients. The electrocardiogram (ECG) of all four patients showed rapid sinus tachycardia with a right ventricular strain pattern. Their chest *x* ray films were in keeping with an acute heart failure and showed cardiac enlargement with mild pulmonary oedema Metabolic acidosis was present in three patients Cardiac muscle enzymes were measured in two patients and were normal. Blood lactic acid concentration was investigated in case 1 and was raised at 145 mg/dl (normal range 5·7–22·0 mg/dl). Three patients had raised serum glucose concentrations (above 6·2 mmol/l) during the first hours of admission. Echocardiography was performed in all patients and yielded normal results. Serum electrolyte concentrations were within normal limits and blood, urine, and cerebrospinal fluid cultures yielded negative results.

Table *Clinical and laboratory findings in the four babies*

Case No	*Skin colour*	*Respiratory rate (breaths/min)*	*Heart rate (beats/min)*	*Liver edge below costal margin (cm)*	*Right ventricular strain*	*Serum cardiac enzymes (U/l)*
1	Pale cyanosis	80	230	6	+	
2	Mild cyanosis	120	220	2	–	CPK 30 LDH 200
3	Pale cyanosis	70	200	3	+	
4	Normal	88	230	4	+	CPK 20 LDH 250

CPK=Creatine phosphokinase (normal 5–130 U/l), LDH=Lactic dehydrogenase (normal 150–370 U/l)

Cases 1, 2, and 4 were treated with digoxin and cases 1, 3, and 4 with furosemide.

The signs of acute heart failure and the sinus tachycardia disappeared in all patients within 24–72 hours. On follow up, repeated physical examination and ECG recordings yielded normal results.

The circumcisions were performed by the same individual and with his cooperation we investigated his procedure.

Among the contents of his bag, a bottle of epinephrine solution 1:1000 was found and apparently this was often used to stop bleeding in circumcision wounds. A sponge soaked in epinephrine was applied to the site of circumcision and left in place for a few hours. We presumed that a considerable amount of epinephrine had been absorbed through the open wound, leading to epinephrine intoxication.

Discussion

Ritual circumcision has been practised by the Jewish people for the last four millenia. The method that should be used is not laid down in the Bible. Rabbis, also known as 'mohels', who perform circumcision, have adopted the technique passed on for generations by their forebears.

Epinephrine increases the strength of ventricular contractions and increases heart rate by beta receptor activity. It also produces peripheral vasoconstriction of the arterioles and precapillary sphincters by its receptor activity.[1] Because of this vasoconstrictive property absorbed epinephrine can considerably reduce cutaneous blood flow. It is effective only against bleeding from small arterioles and does not control venous oozing or haemorrhage from large vessels. Its metabolic effects are hyperglycaemia, lactic acidosis, and rises in free fatty acids in blood.[1]

Epinephrine is inactivated mainly in the liver by the enzymes catechol-o-methyl transferase and monoamino oxidase. The enzymatic capacity of the neonatal liver to metabolise large amounts of epinephrine is unknown.[2]

Brunjes *et al* have speculated that the increased excretion of free catecholamines in the urine of premature infants is due to a deficiency of monoamino oxidase activity.[3] Others have proposed that young infants have a relative deficiency of amine catabolising enzymes.[2]

The effects of an overdose of epinephrine in neonates have been described in a few published reports Local effects on the gastrointestinal tract as a result of an oral administration of epinephrine include gastrointestinal irritation, vomiting, intestinal ileus, and ischaemic damage to the gut wall.[4] Racemic epinephrine given by inhalation has produced paroxysmal supraventricular tachycardia, which was blocked by propranolol.[5] Denton *et al* reported tachycardia, acrocyanosis, and local ischaemia after the local application of a highly concentrated epinephrine solution to a circumcision induced haemorrhage.[6] These symptoms were abolished soon after phentolamine was applied. Cardiac failure has not been described in these reports.

We suggest that the use of topical epinephrine after circumcision should be prohibited and it is hoped that drawing attention to these cases will prevent similar occurrences.

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Methicillin resistant *Staphylococcus aureus* in milk

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SUMMARY Three separate outbreaks of gentamicin and methicillin resistant *Staphylococcus aureus* in a special care baby unit are described. The outbreaks ceased only after a milk bank worker was identified as a carrier of the strain. It is postulated that the infant milk feeds served as a vehicle of spread.

Resistance to methicillin among *Staphylococcus aureus* rapidly followed the introduction of the drug in the 1960s. Recently, problems with gentamicin/methicillin resistant *Staph. aureus* have occurred world wide and they are becoming widespread in the United Kingdom. Outbreaks have only occasionally caused problems in neonatal units. An outbreak of multiresistant methicillin resistant *Staph. aureus* (MRSA) that colonised at least 30 newborn babies in our special care baby unit over a period of 16 months in three separate episodes is reported. The problems encountered in eradicating the strain, until the source was identified, are described.

The outbreak and control measures

The Table shows details of the babies who were possibly infected with the MRSA. Initial nasal and umbilical swabs from babies and nasal swabs from staff revealed six colonised and three infected babies and one staff carrier.

A strict admission policy, barrier nursing, and topical treatment with nasal 1% chlorhexidine cream, 0·33% hexachlorophane talc, and daily chlorhexidine baths produced ineffective control as seven further minor clinical infections (cases 4–10) occurred and a further seven babies became colonised.

Similar treatment failed to eliminate the MRSA

Table *Details of babies with infection due to methicillin resistant* Staphylococcus aureus

Case No	*Age (days)*	*Diagnosis*	*Birth weight (g)*	*Gestational age (wks)*	*Date of isolation of MRSA*	*Site*	*Previous antibiotics*	*Clinical notes*
1	4	Ambiguous genitalia	2080	34	21 08 83 17 01 84	Umbilicus Oral suction	None	Umbilical flare
2	12	Hyaline membrane disease	2100	33	7 09 83	Groin	None	Pustules in groin
3	2	Extrauterine pregnancy	2180	37	10 09 83 13 09 83 21 09 83	Tongue Spots Spots	None	Mouth coated, spots on neck, spots on waist
4	27	Preterm	1150	28	22 09 83 3 10 83	Nose Eye	Amoxycillin	Snuffly nose, watery eye
5	15	Congenital rubella syndrome	1520	37	22 09 83	Umbilicus	None	Moist umbilicus
6	8	Spontaneous pneumothorax	3640	38	2 10 83	Nose	None	Snuffly nose
7	19	Small for dates	1330	37	10 10 83	Pustule	None	Pustule on forehead
8	5	Hyaline membrane disease	1500	31	17 10 83 28 10 83	Umbilicus Pustules Eye	None	Umbilical flare, pustules behind ears, sticky eyes
9	22	Transient tachypnoea	2260	36	24 10 83	Groin	Penicillin+gentamicin	Sore groin
10	87*	Hyaline membrane disease, subglottic stenosis	1280	31	5 12 83 12 12 83 13 01 84	Oropharynx Oropharynx Nose	Ceftazidime Penicillin+gentamicin	Possible chest infection, snuffly nose, osteomyelitis
11	6	Small for dates	1900	36	12 12 83 13 12 83	Pustule Eye	None	Pustule in groin, sticky eyes
12	60	Meningoencephalocele	2840	40	21 07 84	Brain swab (postmortem)	None	Group B *Streptococcus*+ coliforms also isolated from brain at post-mortem examination
13	2	Total aganglionosis	2680	40	1 11 84 12 11 84	Umbilicus Wound	None	Routine swab post-operative wound

MRSA=Methicillin resistant *Staph aureus*
*Admitted to the unit at 30 days

from the staff carrier. Subsequently, fusidic acid cream given nasally eliminated the strain and recolonisation has not occurred.

Case 4 was subsequently admitted to another hospital with possible staphylococcal pneumonia, and MRSA were isolated from his secretions. This first 'serious' infection prompted us to treat all colonised babies with fusidic acid nasal cream as the MRSA was reported to be resistant to other nasal applications. Three weeks later, however, a ventilated baby developed possible osteomyelitis, and oropharyngeal secretions revealed three strains of *Staph. aureus*, which were resistant to fusidic acid, methicillin, and gentamicin, respectively. Treatment with intravenous gentamicin, flucloxacillin, and fusidic acid produced a good clinical result, but the baby remained colonised and subsequently introduced MRSA to another hospital.

The bacitracin resistance was rechecked and the MRSA was found to be sensitive to bacitracin, which was used for nasal carriage and superficial infections One month later the last remaining colonised baby left the unit and no further isolates were recorded for six months when a postmortem brain swab from a child with a meningoencephalocele revealed the MRSA strain. Previously adopted measures were reintroduced. One additional colonised baby was identified and after successful treatment discharged.

Three months later a routine specimen of pooled, pasteurised, expressed breast milk yielded MRSA, and investigation of the milk bank staff revealed one nasal carrier. She was removed from the milk bank and given bacitracin nasal cream and 4% chlorhexidine detergent for bathing. This and a subsequent course of pseudomonic acid failed to eradicate the strain from her nose. Concurrently, an outbreak of loose stools revealed three further colonised babies and subsequently one colonised baby developed a postoperative wound infection with MRSA at another hospital.

MRSA has not been isolated in the 24 months after departure of the last colonised baby and removal of the nurse from the milk bank.

All isolates of MRSA were bacteriophage type 75 and tests performed at the Staphylococcal Reference Laboratory, Colindale, showed the strain to be identical to types found in South Africa and distinguishable from that causing problems recently in the midlands and currently in the south east of England

Discussion

Methicillin/gentamicin resistant *Staph. aureus* have been isolated with increasing frequency in the last few years. Less than 1% of isolates sent to the Staphylococcal Reference Laboratory before 1978 were methicillin/gentamicin resistant, but this figure had risen to 28% by 1983.[1] There are only a few reports of outbreaks in neonatal units.[2-5]

The source of many outbreaks has remained unclear, but staff carriers have been implicated and prolonged carriage by staff may result despite topical treatment.[6] Our medical staff carrier probably acquired the organism by handling colonised babies as she did not spread the organism to babies in the other hospital she attended. We believe the source of our strain was a midwife in the milk bank who had returned from South Africa one month before the first isolate was detected. While in South Africa she had been briefly admitted to hospital after an accident. She remained undetected for 18 months as she had no direct work or social contact with the unit

Milk has been widely reported as a vehicle for the spread of organisms, but we are unaware of other reports implicating it as a vehicle of infection with MRSA. The frequency or degree to which the milk bank nurse contaminated feeds remains unknown. The only contact with the positive milk sample was to remove the sample tube from the pasteuriser and check the tightness of the cap. The sample probably became contaminated from the outside of the tube or cap during transit to or on opening in the laboratory.

Feeding of contaminated milk or contact with contaminated bottles or teats presumably led to either oral or gastrointestinal contamination, or both, with MRSA and subsequent skin colonisation. As previously reported colonisation was more common than infection and most infections were minor.[2 4 5]

Prolonged staphylococcal carriage by staff and patients with possible subsequent re-admission or transfer to another hospital highlights the need for close liaison between medical, nursing, laboratory, and control of infection personnel both within and between hospitals if outbreaks are to be detected early and controlled successfully.

We gratefully acknowledge the help and advice of Drs B A Wharton, C A Smalley, and S E Balmer

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Treatment of campylobacter gastroenteritis

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SUMMARY Twin boys suffered from recurrent diarrhoea due to *Campylobacter jejuni* after entering a day nursery. Stool sampling of all 17 children at the nursery revealed *C. jejuni* in 12. Simultaneous treatment with antibiotics of all children with positive cultures successfully eradicated the infection.

Campylobacter gastroenteritis has been recognised in recent years as a major cause of diarrhoeal diseases in children.[1,2] It accounts for considerable morbidity and may result in chronic diarrhoea and failure to gain weight.[2] This organism has also been responsible for outbreaks in day care centres,[3] where reinfection is common and eradication difficult

We present our experience in the management of an outbreak of campylobacter gastroenteritis in a nursery and suggest a practical approach to eradicate the infection.

Case report

Eleven month old twin boys were referred to us eight weeks after entering a day care centre with a history of recurrent diarrhoea. The diarrhoea had begun two weeks after they had started at the centre. It diminished when the mother removed them for periods of several days, only to return on re-admission. The diarrhoea consisted of between four and nine yellowish-green, soft, bulky stools each day for periods of up to two weeks. Their body weight dropped from the 75th to the 25th centile. *Campylobacter jejuni* was cultured from one infant; no other enteric pathogen was isolated

Erythromycin estolate 50 mg/kg/day was administered to both children for seven days, with complete resolution of symptoms. Repeated stool cultures for *C. jejuni* after the treatment yielded negative results Two weeks later, after re-entering the centre, diarrhoea occurred again in both children and *C. jejuni* was again isolated. Clinical and laboratory recovery was again observed after a second course of treatment.

A further episode of diarrhoea occurred 10 days after stopping treatment, and *C. jejuni* was isolated from the stools of both boys. On this occasion, the father, who was a physician, collected stool samples from the other children at the nursery *C. jejuni* was isolated in the stools of 12 of the 17 children. All these children had suffered from at least one period of diarrhoea during the past two months. By the time of stool sampling, however, eight of the children were already asymptomatic.

All children with positive stool culture were treated simultaneously with a course of erythromycin. A week later stool cultures from these children yielded negative results. From then until the end of the school year (eight months) no further outbreaks of diarrhoea occurred in the centre.

Discussion

Outbreaks of gastroenteritis among children in day care centres are well known.[4] Close personal contact and poor hygiene in young children, especially in those who are not yet toilet trained, enable the spread of enteric pathogens. The problem of reinfection by the same agent ('ping pong mechanism') is common among these children and can ruin efforts to eradicate the infection.

Recently, attention has been called to the role of *C jejuni* in infectious diarrhoea in children, including outbreaks in day care centres.[1,3] Relapses of this infection are documented in our patients, as reported before[5,6] The high rate of relapse usually results from reinfection. This is caused by the prolonged excretion of the organism among untreated children, lasting up to seven weeks.[5] On the other hand, stool cultures of all treated patients yielded negative results within 48 hours.[5] Our patients indeed showed that simultaneous treatment is effective in preventing reinfection as it caused concomitant eradication of the infection in all the children.

It is concluded that in a nursery with multiple cases of campylobacter enteritis stool cultures should be taken from all children, including those who are asymptomatic at that time, because it is necessary to treat *simultaneously* all children whose cultures yield positive results. This approach is an effective method for eradicating the infection.

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Commentary

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It is often forgotten that antimicrobial drugs can sometimes be used to control the spread of gut infection. This 'epidemiological' use has a chequered history. Most often non-absorbable antibiotics, such as neomycin, have been employed to blanket an outbreak, especially of *Escherichia coli* gastroenteritis, and with variable results. Sometimes the outbreak was apparently controlled and at other times the attempt failed completely, certainly, antibiotic prophylaxis should not be used in this way unless combined with a rigorous attempt to tighten up normal hygienic methods of cross infection control.

This description of the control of campylobacter gastroenteritis in a day care centre makes a useful point. Features of this infection that perhaps make for a favourable outcome are:

(1) Erythromycin certainly seems to render stool cultures negative very quickly, usually within 48 hours of starting the drug (their references 1 and 6)

(2) The duration of carriage may be quite long without treatment, although 90% of patients do become negative spontaneously within two months

(3) Campylobacter diarrhoea, although usually short lived, can be prolonged or recurrent, and it is patients with diarrhoea who pose most risk to their contacts. Although eight of the 12 contacts with positive stools were asymptomatic at the time of sampling, all of them had had recent diarrhoea.

Co-trimoxazole red cell aplasia in leukaemia

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SUMMARY A 4 year old boy with acute lymphoblastic leukaemia developed a pure red cell aplasia 13 months after entering remission and while on maintenance chemotherapy. Co-trimoxazole was also being administered for prophylaxis against *Pneumocystis carinii* infection. When co-trimoxazole was stopped the red cell aplasia resolved.

Co-trimoxazole (sulphamethoxazole and trimethoprim) provides effective prophylaxis against *Pneumocystis carinii* infection[1] and is therefore commonly used during treatment for childhood acute lymphoblastic leukaemia. Haematological toxicity, particularly neutropenia and thrombocytopenia, has been described with co-trimoxazole,[2 3] but selective aplasia of the bone marrow erythroid series is extremely rare and has not previously been reported in acute lymphoblastic leukaemia. We report a case of pure red cell aplasia that occurred in a child on maintenance treatment for acute lymphoblastic leukaemia and that completely resolved when treatment with co-trimoxazole was stopped.

Case report

A 4 year old boy developed acute lymphoblastic leukaemia in July 1983 and remission was promptly obtained using vincristine, prednisone, adriamycin, and L-asparaginase. In September 1983, after consolidation treatment, maintenance treatment with three weekly sequences of vincristine, prednisone, 6-mercaptopurine, and methotrexate was given. Treatment with co-trimoxazole (as trimethoprim 40 mg daily) was begun for pneumocystis prophylaxis once remission had been obtained

Haemoglobin concentrations remained satisfactory during early maintenance treatment and a bone marrow examination in February 1984 (because of persistent neutropenia) showed hyperplastic megaloblastic erythropoiesis but no evidence of acute lymphoblastic leukaemia.

After 13 months in remission (November 1984) the haemoglobin fell 64 g/l over a five week period (Figure). The red cells were normochromic and normocytic (mean corpuscular volume 88 fl, mean corpuscular haemoglobin 31·1 pg, and mean corpuscular haemoglobin 354 g/l). The reticulocyte count was less than 0·1% and white cell and platelet counts yielded normal results A previous reticulocyte count of 3% had been recorded six months earlier Serum folate and vitamin B_{12} concentrations were normal. One unit of packed red cells was transfused but the subsequent rise in haemoglobin was only transient. Transfusions were required at roughly monthly intervals to maintain an adequate haemoglobin. The reticulocyte count always remained below 0·1%. White cell and platelet concentrations remained unchanged throughout this period compared with previously. Bone marrow examination in March 1985 showed markedly hypoplastic erythropoiesis with only 4% erythroblasts. An occasional cell was megaloblastic. Serum folate and vitamin B_{12} concentrations were again normal. White cell and platelet precursor series were normal, with no evidence of leukaemic relapse. A further two units of packed cells were transfused and co-trimoxazole was stopped in case this was responsible for the red cell aplasia.

Over the next six weeks the patient's haemoglobin remained stable, ranging between 116 and 127 g/l.

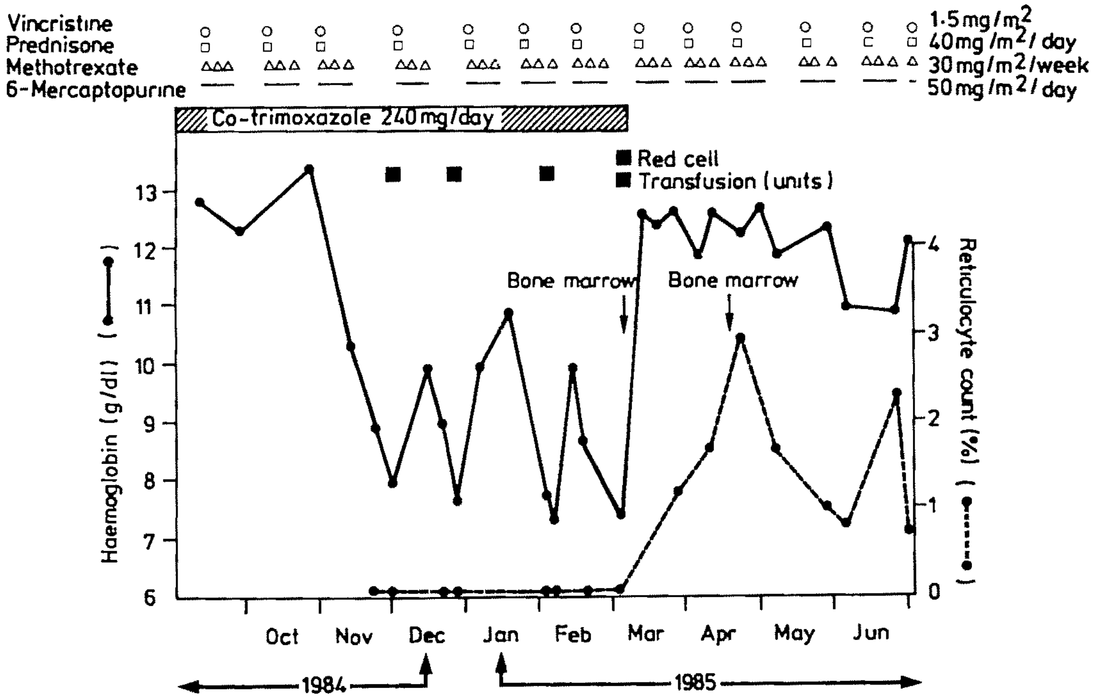

Figure *Treatment regimen in a case of red cell aplasia. Bone marrow examinations and packed red cell transfusions are shown.*

The reticulocyte count rapidly increased to a peak of 3·7% in mid-April. Repeat bone marrow examination six weeks after stopping of treatment with co-trimoxazole showed complete resolution of red cell aplasia with 28% erythroblasts, indicating normal erythropoiesis. The haemoglobin and reticulocyte counts have continued to remain at satisfactory levels and no further blood transfusions have been required. Co-trimoxazole has not been restarted.

Discussion

Selective erythroid aplasia has been reported in two children receiving combination therapy for acute lymphoblastic leukaemia,[4] being reversible on stopping treatment in one patient Neither patient was exposed to co-trimoxazole. Erythroid hypoplasia developed in an adult patient with Crohn's disease on long term treatment with co-trimoxazole.[5] Drysdale has reported a child with acute lymphoblastic leukaemia, on similar treatment to our patient, who developed transfusion dependent anaemia when co-trimoxazole prophylaxis was begun.[6] This patient also took sodium valproate for epilepsy and this drug was thought to be contributory. A red cell aplasia was not proved by bone marrow examination

Our patient's red cell aplasia developed after 13 months of treatment with co-trimoxazole. Maintenance chemotherapy remained unchanged before, during, and after the episode. There was no exposure to other drugs over the entire period. Complete resolution of the bone marrow abnormality occurred after stopping treatment with co-trimoxazole.

We believe that this is the first reported case of red cell aplasia attributable to treatment with co-trimoxazole in a child with acute lymphoblastic leukaemia. Red cell aplasia induced by co-trimoxazole should be considered in this disease should unexplained anaemia develop.

We thank Dr MEJ Beard, haematologist, for his help with this case

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Personal practice

Pitfalls in the management of epilepsy

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Recent publications on childhood epilepsy and personal experience at the National Centre for Children with Epilepsy both suggest that the management of children with this disorder remains an area of clinical practice in which special difficulties are encountered. The following remarks are relevant mainly for children of school age Emergency situations are not considered.

Differential diagnosis

Different types of attack may be superficially similar and confusion between epileptic and non-epileptic attacks may well occur. It seems that various types of non-epileptic attack continue to be misdiagnosed as epilepsy. In one recent series a quarter of patients referred to an epilepsy clinic had been misdiagosed in this way [1] Faints and breathholding attacks, especially those that end with convulsive movements, were often misconstrued as epilepsy, as were aggressive outbursts, sleep disorders, and atypical forms of migraine.

Accurate diagnosis should be possible from a precise description of each attack (from the very first change to full recovery) and from the circumstances in which the attacks occur as the various types of attack have characteristic features.[2] If the true nature of the child's attacks remains obscure, in spite of a precise description, prolonged electroencephalogram (EEG) recordings during attacks can be helpful.[3]

Sometimes the opposite problem is encountered—that is, seizures are not recognised as such and are diagnosed as non-epileptic attacks, usually of a psychological type. This risk is greatest with non-convulsive seizures and is particularly likely to occur if the wide range of seizure types described in the international classification of seizures[4] is not appreciated.

Seizure type

Seizures are often not accurately classified. All non-convulsive seizures are sometimes referred to as 'petit mal', but within this broad category there exist very different forms of seizure—notably, absence seizures and complex partial seizures. The similarity of these two seizure types—that is, that both are characterised by fairly brief impairment of consciousness—should not obscure the important differences between them. Absence seizures are usually inherited, do not require radiological investigation, often respond to valproate or ethosuximide (but not carbamazepine), and usually remit spontaneously by early adult life. In contrast, structural cerebral lesions need to be considered in complex partial seizures. These seizures may well be helped by carbamazepine (or perhaps valproate) but often persist, and a proportion will need surgery. Mode of onset and termination and duration of the seizure are usually very different in these two types of attack.[5] Absence seizures begin and end abruptly and last five to 15 seconds; complex partial seizures often begin with an aura and last 30 seconds to two minutes, with gradual return to normality. Automatisms are seen in both types of seizure but are less complicated in the absence type.

The way in which a generalised tonic-clonic seizure begins may be difficult to determine, especially during the night, but can contain important information. Generalised convulsions with initial subjective or objective changes to suggest a partial (focal) onset need to be investigated and treated as partial seizures. Generally, they have a less good prognosis than convulsions that are generalised from the outset. Orofacial symptoms and signs should be sought at the onset of the seizure, especially if convulsions occur during sleep in an otherwise neurologically intact child, to identify benign centrotemporal epilepsy of childhood,[6] which, unlike other partial epilepsies, will almost certainly remit spontaneously by puberty.

Underlying cause

The cause of a child's epilepsy may not be obvious but needs to be carefully considered. Otherwise, opportunities may be missed to provide much needed explanations to parents (who might blame themselves or worry needlessly about possible sinister causes) or to provide genetic counselling in those conditions for which this is appropriate. Computed tomography is required if there is clinical or EEG evidence of a localised abnormality, but a negative finding does not exclude a structural brain lesion and repeated high quality scanning at intervals may well be necessary.

EEG investigations

EEG continues to be a potential source of confusion, mainly because of inadequate provision of services or misrepresentation of the findings. EEG studies should be designed to answer specific clinical questions, and interpretation of the findings needs to be meaningful and relevant.[7] A comprehensive EEG service should be able to answer such questions as the following:

What is the nature of the child's attacks? EEG recordings during attacks are necessary to avoid misleading inferences from interattack EEG abnormalities, which may well be no more than nonspecific unusual features without pathological importance.

What type of seizure does the child have?

Is there a clue to underlying cause?

Are precipitating factors identifiable, or other patterns of seizure occurrence?

Is the child having subtle seizures clinically difficult to detect?

Anti-epileptic drug treatment

Standards of practice in the use of antiepileptic drugs have improved in recent years, perhaps especially in paediatrics, but difficulties in their use are often experienced. When to start drugs can be a difficult decision.[8] It is generally inappropriate to introduce treatment with drugs after a single seizure or even after several mild seizures have occurred. The available range of antiepileptic drugs may be confusing, but certain basic principles can help.[9] Treatment with a single drug is preferable as combined treatment is usually unnecessarily complicated and may produce unwelcome interactions or adverse additive effects. Valproate or carbamazepine are effective in most cases, but choice of drug depends on seizure type. Both these drugs are broad range, but carbamazepine is ineffective in primary generalised seizures other than generalised tonic-clonic seizures. The place of valproate in the partial epilepsies is being investigated at the present time.

When to withdraw treatment can be a difficult issue, especially when there is particular concern about relapse (especially in teenagers wanting a driving licence), but generally it is appropriate to withdraw treatment cautiously if the child has been free of seizures for two years. EEG is not a good guide to time of withdrawal. A normal record gives no guarantee that relapse will not occur Conversely, persistent EEG abnormalities do not necessarily predict relapse. The decision is essentially a clinical matter

Seizures may persist in spite of drug treatment.[10] In this situation certain possibilities should be considered. These include: mismatch between seizure type and drug; too high or too low dosage; non-compliance (this is common especially where confidence has been lost); progressive underlying disease (uncommon); and emotional or other environmental precipitants of seizures, which are commonplace Epilepsy in the severely retarded is generally difficult to control because of the serious underlying brain disorder.

Prognosis

Parents naturally almost always ask if their child will grow out of his seizures. This can be a difficult question to answer, but the clue lies in establishing as far as possible the child's precise type of epilepsy and possible associated disorder. Generalisations about prognosis are unhelpful in such a mixed group of disorders as the epilepsies

Sometimes it is possible to be very reassuring about the future. Almost certainly benign centrotemporal epilepsy of childhood (a common form of childhood epilepsy) will stop by puberty. Eighty per cent or more of absence seizures and a similar proportion of primary generalised tonic-clonic seizures may well remit by early adult life. A child who is neurologically intact apart from the seizure disorder has a very good chance of growing out of his epilepsy by early adult life or thereabouts. In contrast, epilepsies associated with mental retardation carry a poor prognosis for seizure control, although remission is not impossible. Partial epilepsies hold an intermediate position. Their prognosis is determined largely by the underlying cause.

Behavioural aspects

Often the relation between epilepsy and behaviour is misunderstood. Parents, teachers, and doctors often fear that behavioural disturbance or poor intellectual development is likely This is not so The behaviour of most people with epilepsy is no different from that of anyone else. There is no justification for the notion of 'the epileptic personality' as an inevitable consequence of having seizures.[11] In particular, contrary to popular and professional belief, the behaviour of people with epilepsy is not unpredictably explosive; in fact seizures very rarely take the form of aggressive outbursts.[12]

The typical psychological problems of people with epilepsy are depression and anxiety caused by unhelpful and uninformed social attitudes. Treatment with antiepileptic drugs, especially barbiturates, may also cause depression and irritability. In other words, behavioural or emotional upset is not inevitable but can be prevented or treated. Difficult behaviour in children with epilepsy is almost always the result of mishandling at home or at school, including overrestriction or overpermissiveness The same measures should be applied as in other children. In those children with epilepsy at special risk of educational underachievement it is also important to adopt a positive approach based on careful assessment of the various psychological and physical factors that may be relevant [13]

Comprehensive care

It is easy to become preoccupied with seizure control by means of drugs to the exclusion of other important aspects of the child's situation.

A comprehensive view needs to be taken of any child with epilepsy, especially if seizures have persisted for some time Attitudes and expectations of parents, teachers, other children, and the child himself have to be assessed as they may offer serious barriers to academic and social development as well as seizure control. Where particular problems have developed special help may be needed and this is best provided in special epilepsy clinics or, in particularly complicated cases, epilepsy centres where the efforts of physicians, psychologists, social workers, and others can be coordinated. It is impossible to provide such help without much time and effort being available. A busy general outpatient clinic cannot meet these complicated needs.

Communication problems

A serious pitfall in the care of children with epilepsy seems to be poor communication. Evidence from various sources, such as the study by Holdsworth and Whitmore,[14] indicates that enormous communication problems often exist between the various people involved in the care of the child with epilepsy. Only the closest cooperation and free exchange of information between general practitioner, hospital doctors, parents, teachers, and others will avoid the confusion and misunderstanding of what the child requires. Standardisation of terminology would help to some extent. There is much to be said for abandoning the ambiguous terms such as 'grand mal', 'petit mal', 'major', and 'minor' attacks in favour of the clinically more precise terms recommended in the international classification of seizures[4] mentioned earlier. In addition, however, respective roles need to be defined and efforts coordinated. This seems to be difficult to achieve, especially in some parts of the country where there are less resources or interest than elsewhere but the effort is well worth while.

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Current topic

The role of bicarbonate and base precursors in treatment of acute gastroenteritis

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Widespread use of oral glucose-electrolyte rehydration solutions (ORS) has resulted in a dramatic decrease in the morbidity and mortality associated with childhood gastroenteritis, regardless of its aetiology. Nevertheless, diarrhoeal disease remains the most common cause of death of children in developing countries, and current research efforts are directed towards optimising the efficacy of ORS, aiming for both simplicity and economy. Controversy regarding the 'ideal' sodium and glucose concentration continues to the extent that different formulations are now recommended in the developing and industrialised world. The inclusion of bicarbonate or a base precursor (citrate, acetate, or lactate) in ORS is generally assumed to be necessary, both for promotion of water and sodium absorption and correction of acidosis. This issue, however, has received little critical attention since the formal introduction of oral rehydration therapy. We have reviewed the available evidence from animal and human studies and conclude that there is little evidence to support the inclusion of bicarbonate or a base precursor in ORS.

Historical considerations

Intravenous treatment. As early as 1832 Latta recommended intravenous saline containing 'two scruples of subcarbonate of soda' for the treatment of cholera and its associated acidosis.[1] A similar regimen with intravenous sodium acetate or bicarbonate was used by 1910 by Sellards.[2] This treatment decreased the mortality from renal failure associated with cholera. Acidosis in infantile diarrhoea of other causes was also shown to improve after administration of bicarbonate.[3] Powers recommended bicarbonate in his plan of treatment for the 'intestinal intoxication of infants' in 1926,[4] and Hartmann used sodium lactate to relieve acidosis in diarrhoeal disease in 1938.[5] None of these studies, however, attempted to answer the important question as to whether rehydration with base was superior to rehydration with saline alone.

The use of parenteral bicarbonate was not without its problems. In the 1940s Rapoport *et al* recommended vigorous rehydration with saline containing sodium bicarbonate but without potassium and reported a 'post-acidotic state' in children whose diarrhoea had improved and in whom recovery seemed imminent.[6] The clinical syndrome he described of lethargy, irritability, abnormal cardiac function, intracranial haemorrhage, generalised oedema, and tetany can be attributed to the alkalosis and electrolyte disturbance (hypokalaemia, hypocalcaemia, hypophosphataemia, and hypernatraemia) after excessive rapid administration of sodium and alkali.

Oral treatment. Darrow was the first to recommend oral rehydration with a glucose-electrolyte solution as an alternative to intravenous fluids. Although all the children in his original study had low serum bicarbonate concentrations, these returned to normal after treatment with solutions containing lactate (53 mmol/l), even in the most severe cases. Although this often took more than 24 hours, acidosis did not recur after rehydration began, and alkalosis and the 'post-acidotic state' were never observed. Further studies confirmed these findings, leading Darrow and colleagues to conclude that additional bases such as sodium bicarbonate were seldom if ever required for the treatment of acidosis in diarrhoeal disease of infancy.[7] Furthermore, these investigators recognised that if bicarbonate was given rapidly or in large amounts the condition described by Rapoport could occur.

Since those early days, the use of oral rehydration solutions has rapidly increased. Bicarbonate or a base precursor is included in the World Health Organisation (WHO) ORS and in commercially manufactured ORSs in the United Kingdom (Table 1) and throughout the world, on the premises that

Table 1 *Composition of WHO and commercial ORSs (mmol/l)*

	WHO	*WHO citrate*	*BNF**	*Dioralyte†*	*Rehidrat‡*	*Dextrolyte§*
Bicarbonate	30		18	18	20	
Citrate		10			9	
Lactate						18
Sodium	90	90	35	35	50	35
Chloride	80	80	37	37	50	30
Potassium	20	20	20	20	20	13
Glucose	111	111	200	202	91	200
Sucrose					94	
Fructose					2	

**British National Formulary*, Sodium Chloride and Glucose Oral Powder Compound
†Armour Pharmaceutical Co Ltd
‡Searle Pharmaceuticals
§Cow and Gate Ltd

(a) bicarbonate enhances sodium and water absorption and (b) the metabolic acidosis of acute diarrhoea requires correction with exogenous base. Justification for the continued use of bicarbonate or base precursor in ORS must be supported by evidence for at least one or preferably both of these statements.

Effect of base on intestinal sodium and water transport

Bicarbonate stimulates water and sodium absorption in the normal human jejunum and ileum.[8] The magnitude of this effect on sodium absorption in the human jejunum is comparable with that of glucose and independent of luminal pH.[9] Short chain fatty acids, such as the base precursor acetate, share the ability of bicarbonate to stimulate sodium and water absorption in the human small intestine.[10]

Although bicarbonate has similar effects on water and sodium absorption in the normal rat small intestine,[11] we have shown that bicarbonate and the base precursors acetate and citrate are unable (unlike glucose) to reverse water and sodium secretion induced by cholera toxin (Unpublished observations). These findings suggest that bicarbonate may not be beneficial with respect to the promotion of water absorption in the enterotoxin mediated diarrhoeas

Role of base in the correction of metabolic acidosis

It is now generally accepted that in metabolic acidosis of childhood administration of bicarbonate should be reserved for conditions in which endogenous production or conservation of bicarbonate is inadequate to restore normal pH. Examples of such specific disorders include salicylism, prolonged diarrhoea, disorders of organic and amino acid metabolism, and renal tubular acidosis In acute hypoxia and prerenal or circulatory failure bicarbonate is only recommended when pH fails to correct after restoration of adequate intravascular volume. Similarly, children with diabetes with ketoacidosis do not require bicarbonate providing adequate insulin and fluids are given and cardiovascular and renal function is normal, unless blood pH falls below 7·2.[12]

Metabolic acidosis during acute diarrhoea is generally attributed to bicarbonate loss in the stool, which results in loss of total blood buffering capacity. In addition, when dehydration is severe and renal plasma flow falls excretion of hydrogen ions and regeneration of bicarbonate is impaired. Also poor perfusion of peripheral tissue may contribute to a lactic acidosis. Acidosis is more likely to complicate cholera than other acute diarrhoea, as the stool concentration of bicarbonate is higher than in rotavirus or enterotoxigenic *Escherichia coli* diarrhoea and dehydration more pronounced (Table 2).[13,14] Despite these theoretical considerations and the common finding of a reduced serum bicarbonate concentration in acute diarrhoea, mean arterial pH is often normal.

Thus, providing perfusion is maintained, renal compensation ensures that acid-base state will normalise with rehydration *without* additional base in the vast majority of cases of acute gastroenteritis

In severely dehydrated or acidotic patients

Table 2 *Electrolyte composition of stool in childhood gastroenteritis*

Aetiology	*Stool electrolytes (mmol/l)*			
	Sodium	*Potassium*	*Chloride*	*Bicarbonate*
Cholera	101*	27	92	32
	88†	30	86	32
Rotavirus	37†	38	22	6
Enterotoxigenic *Escherichia coli*	53†	37	24	18
Non-cholera diarrhoea	56*	25	55	14

*Reference 13
†Reference 14

(pH<7·2), in those with persistent high volume diarrhoea, and in those with impaired renal function and worsening metabolic acidosis the administration of intravenous base such as sodium bicarbonate is indicated and may be life saving Correction of acidosis with parenteral sodium bicarbonate must be performed with caution to avoid its detrimental effects.[12]

Clinical observations

There is little clinical evidence to support the inclusion of base in the treatment of acidosis and dehydration in acute diarrhoea. Indeed, most regimens for intravenous rehydration are effective despite the omission of bicarbonate.[15] In a controlled trial in Capetown Heese compared a mildly alkalinising intravenous solution (26 mEq/l lactate) with or without additional sodium bicarbonate for treating children with acute gastroenteritis who were acidotic and 5–10% dehydrated. Those who received additional base regained normal pH, carbon dioxide tension, and serum bicarbonate more quickly than those who did not, but no ill effects were suffered by the latter group, and both groups were biochemically identical by 24 hours.[16]

Early uncontrolled studies based in hospitals have shown equal effectiveness in rehydration but slower correction of acidosis when comparing a labon-gur (common salt and brown sugar) ORS without bicarbonate with the WHO solution [17] An uncontrolled study based in the community in the Punjab has shown successful treatment of acute diarrhoea in children and a substantial reduction in mortality even when both sodium bicarbonate and potassium chloride were omitted from the ORS.[18] Similarly, rice water without electrolyte additives has been used successfully in the treatment of infantile gastroenteritis.[19] In Cardiff 90 children admitted with gastroenteritis and reduced serum bicarbonate concentrations were adequately treated with intravenous or oral rehydration solutions without bicarbonate.[15]

Controlled trials examining the value of base in ORS are few and are outlined in Table 3 In a recent clinical trial in Bangladesh Islam compared the efficacy of ORS with and without bicarbonate.[20] He showed that while correction of serum bicarbonate was slower in the children receiving the solution free of bicarbonate compared with the control group (WHO-ORS) during the first 24 hours, there was no difference at 48 hours. The delayed return of plasma bicarbonate to normal almost certainly has no clinical relevance as the patients were rehydrated, with good urine output and no clinical evidence of acidosis. A double blind controlled trial in the

Table 3 *Recent controlled trials of bicarbonate and base precursors in ORSs*

Study	*Location*	*Age range*	*(n)*	*ORS tested*	*Result*		
					Rehydration	*Correction of acidosis*	*Stool volume*
Islam[20]	Bangladesh	<5 years	(98)	WHO–ORS *v* WHO–ORS without bicarbonate	Similar	Slower (serum bicarbonate) with WHO–ORS without bicarbonate at 24h, same at 48h	NS*
Clements[21]	Honduras	3–18 months	(61)	WHO–ORS *v* simple sugar salt solution	Similar	Slower (total carbon dioxide) with sugar salt solution, but similar at 48h	
Patra[23]	Calcutta	2·5–72 months	(40)	WHO–ORS *v* ORS acetate	Similar	Similar	NS*
Islam[27]	Bangladesh	2–10 years > 10 years	(26) (14)	WHO–ORS *v* ORS citrate	Similar	Similar (total carbon dioxide) at 4, 24, and 48h	NS*
Hoffman[28]	Jakarta	3–82 years	(130)	WHO–ORS *v* ORS citrate	ORS citrate superior	Faster (total carbon dioxide) with ORS citrate	Less with ORS citrate
Islam[30]	Bangladesh	<5 years	(94)	WHO–ORS *v* ORS citrate	Similar	Slower (serum bicarbonate) with ORS citrate at 24h, same at 48h	NS*

*Trend to higher stool volume with ORS containing bicarbonate

Honduras showed that a simple oral sugar/salt solution without bicarbonate will correct even pronounced acidosis (total carbon dioxide <10 mmol/l) as effectively, though slightly more slowly, than the WHO solution.[21] We have recently completed a double blind controlled trial comparing British National Formulary ORS (Table 1) with an identical solution in which bicarbonate was replaced by chloride. In 40 children with gastroenteritis inclusion of bicarbonate offered no clinical or biochemical advantage (Unpublished observations).

Practical problems with bicarbonate

Although intravenous solutions containing bicarbonate have been widely used, they must be autoclaved under a high carbon dioxide pressure, making production of sterile solutions difficult.[22] Regarding ORS, bicarbonate is often unavailable in developing countries and adds to the bulk and expense of ORS sachets. On exposure to high humidity or heat bicarbonate in ORS powders may form furfural compounds with glucose, causing decomposition of these substances, colouring the reconstituted solution brown, and making it less palatable.[23] Although this problem can be overcome by using chemically treated (encapsulated) sodium bicarbonate, this increases the cost of production.[24] In aqueous solution bicarbonate may decompose to form carbonate Additionally, flavouring agents, such as citric acid, used in some commercial formulations react with bicarbonate to form carbon dioxide and water with a resultant sharp fall in bicarbonate concentration in the solution.[25] These difficulties associated with the use of bicarbonate have prompted the search for an alternative base.

The use of base precursors

The base precursors acetate, citrate, and lactate have been incorporated in intravenous and oral rehydrating fluids,[22] although a possible drawback is that their metabolism may be seriously impaired in severe dehydration with circulatory compromise.

Controlled clinical trials of base precursors in ORS are outlined in Table 3. Patra, in a double blind controlled trial of infants with diarrhoeal dehydration and reduced plasma carbon dioxide concentrations (mean 14–15 mmol/l) found that ORSs containing acetate or bicarbonate were equally effective in correcting dehydration and acidosis but that patients were less willing to take solutions containing bicarbonate, which had discoloured brown [23] Acetate salts, however, being highly hygroscopic, have a shorter shelf life than those containing sodium bicarbonate[26] and turn to a jelly or gum like material by 12 hours at 37°C and more quickly if a small amount of water is added. Their use in powdered ORS, therefore, is not recommended.

In contrast, citrate is stable in tropical countries; no discoloration occurs during storage at up to 60°C for up to 3 years.[24] Islam showed that an ORS containing tribasic sodium citrate compared favourably with the WHO ORS containing sodium bicarbonate, with respect to both its ability to rehydrate and to correct acidosis.[27] A similar study in Jakarta concluded that the trisodium citrate based ORS resulted in less vomiting and stool output than the bicarbonate based ORS. Correction of serum carbon dioxide was more rapid with the citrate based ORS, despite a significantly lower serum carbon dioxide concentration on admission in the patients receiving this solution.[28] Several other unpublished clinical trials conducted by the WHO diarrhoeal diseases control programme have compared citrate ORS and bicarbonate ORS. Although stool volume was higher when bicarbonate ORS was used in cholera, there was no difference in non-cholera diarrhoeas.[29] Islam has recently investigated the use of tripotassium citrate monohydrate as a substitute for both sodium bicarbonate and potassium chloride in the WHO solution.[30] The solution containing citrate resulted in slower correction of serum bicarbonate, but there was no difference between the groups at 48 hours.

Although several clinical studies suggest that citrate containing ORS may result in slightly lower stool volumes than equivalent bicarbonate containing ORS, the advantage of citrate over a solution without base has not been investigated.

It has been argued that the greater stability of lactate over citrate salts makes the former preferable for use in powdered ORS, but lactate containing solutions support mould growth, which may cause deterioration of glasswear and alter shelf life of the solution.[21]

Conclusions

When considering ORSs, particularly for use in developing countries, our prime concerns must be simplicity, effectiveness, and economy. Bicarbonate and base precursors (acetate and citrate) pose problems with respect to availability, cost, packaging, and stability. Further, they are of dubious benefit therapeutically, both for correction of acidosis and rehydration. Exclusion of these substances would decrease the production cost of prepackaged ORS, make preparation in the home easier, and possibly result in earlier beginning of oral rehydration therapy, leading ultimately to the prevention of serious dehydration.

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British Paediatric Association

Minutes of the Annual General Meeting

The Annual General Meeting of the British Paediatric Association was held on Wednesday, 16 April, 1986 at the University of York. The President, Professor J O Forfar, took the chair.

1 OBITUARY
The meeting stood in memory of the Members who had died since the last meeting: Dr Joan Angus (previously a member of the BPA); Sir John Brotherston (Honorary Member); Dr W E Crosbie (Honorary Member); Dr L A Hawkins; Dr Elizabeth Hervey; Dr H R Jolly (Honorary Member); Dr R Kessel; Dr R C Lightwood (Honorary Member and Past President); Dr E d'H Lobo; Professor R McIntosh (Honorary Member); Dr D M Morgan, Professor C Salazar de Sousa (Honorary Member); Dr J Thomson, (previously a member of the BPA); Dr Shelagh Tyrrell, Mr D J Waterston (Honorary Member).

2 MINUTES OF THE 1985 ANNUAL GENERAL MEETING
The minutes of the meeting held on 18 April 1985, which had been circulated to members in March in the Annual Report, were accepted and signed as a correct record.

3 ELECTIONS
The meeting ratified Council's election of: Dr W J Appleyard to serve as Honorary Treasurer 1986–88 and Professor R D H Boyd to serve as Chairman-Elect of the Academic Board 1986–87 and Chairman of the Academic Board 1987–1990

4 ELECTION OF NEW MEMBERS
Dr Pamela Davies, Dr Dorothy Egan, Dr H McC Giles, Sir Raymond Hoffenberg, Lady Limerick, Professor R G Mitchell, Sir David Innes Williams, Dr Olive Scott and Professor I J Carré had been nominated as Honorary Members, together with one hundred and five Ordinary Members, seventeen Overseas Members and forty eight Associate Members. The meeting approved the nominations and the new members were duly elected

5 PRESIDENT'S REPORT
The President's Report had been circulated to members in March in the Annual Report and was approved by the Annual General Meeting.

The President thanked the Officers of the Association, the members of Committees and Working Parties and the members of the secretariat for their valuable contributions to the affairs of the BPA.

6 TREASURER'S REPORT
The Treasurer presented the Accounts for the period 1 January to 31 December 1985 These had been circulated to members with the Annual Report and had subsequently been audited. Expenditure had increased owing to the growing activities of the Association, the need for more staff and the move to the new and larger premises in St Andrews Place. The high level of interest rates during the year had yielded a substantial return which was not likely to be maintained; the Association's investments policy was under review. Donations from research trust funds and from industry funded a number of secretariat posts and were a valuable contribution to the work of the BPA. The Association was grateful to the editors of the *Archives of Disease in Childhood*, Professor S R Meadow and Dr H B Valman The level of sales of the journal had been maintained and the Association's share of the profits on sales during 1985 was substantial. Although income from this source would be lower in future following changes in the marketing of the journal, the high levels of receipts from the *Archives* over recent years had enabled the Association to build up its reserves.

Following its Appeal the Royal College of Physicians of London would make over to the BPA £15,000 a year for four years to help towards the running costs of the new offices £50,000 had been spent on furniture and equipment.

The Honorary Treasurer thanked Mr Michael Ray, the Association's financial adviser, and the secretariat, for their work in preparing the accounts.

The Honorary Treasurer's verbal report and the circulated Accounts for 1985 were approved.

7 MEMBERS' SUBSCRIPTIONS
The meeting agreed that the annual subscription rate for Ordinary Members should be increased to a point between £90 and £97 from 1 January 1987,

with increases pro rata for the other rates In due course Council would ratify the definite subscription.

8 RULES OF THE ASSOCIATION

The meeting considered amendments to the Rules of the Association which had been circulated to members in March in the Annual Report. Proposed amendments to:

(a) Rule 6 Executive Committee; and
(b) Rule 8 (e) General Meetings were accepted.

9 REPORT OF THE ACADEMIC BOARD

The Report of the Academic Board which had been circulated to members in March in the Annual Report was received. The President expressed the Association's gratitude to the Academic Board for its valuable contribution to the work of the BPA.

10 REPORTS FROM STANDING COMMITTEES, WORKING PARTIES, PAEDIATRIC SPECIALTY GROUPS AND OUTSIDE BODIES 1985–86

The meeting received reports which had been circulated in the Annual Report to members in March. All those who had served were thanked for their valuable contribution to the work of the Association.

Dr W A M Cutting reported that the British Paediatric Tropical Child Health Group had been reconstituted under the title of the British Paediatric International Child Health Group. The group, to be convened by Dr M C K Chan would extend the functions of the former group to include some of those of the Third World Forum.

11 ANNUAL MEETINGS 1991–94

The meeting noted that the 1985 AGM had agreed that the 1990 Annual Meeting would take place at the University of Warwick from 3 to 7 April.

The Chairman of the Academic Board reported that a meeting of the conveners of the paediatric specialty groups and members of the Academic Board and Executive Committee had been held at the University of Warwick on 1 October 1985. The exhibition area and facilities for parallel sessions would allow greater flexibility than those at the University of York and the meeting had recommended that future meetings be held there. The AGM agreed that the Annual Meetings in 1991–94 should take place at the University of Warwick.

Archives of Disease in Childhood, 1987, **62**, 98–103

Correspondence

Medical evidence in child abuse

Sir,

Taitz and King suggest that the existence of 'speech delay' may be offered as evidence of serious deprivation in care proceedings.[1] We feel that the relations between language development, deprivation, and child abuse are more complex than Taitz and King imply

(1) 'Speech delay' is an imprecise term Does it refer to poor articulation, limited vocabulary, immature syntax, inadequate social use of language, or poor comprehension? When is 'delay' significant? Speech therapists report 'delay' at varying levels on language testing, from less than −1 to −2 standard deviations from the mean

(2) There is wide variation in the rate of language acquisition even among normal children growing up in stable families,[2] and a substantial part of this variation is determined by genetic and constitutional factors.[3]

(3) Although much has been written in a descriptive sense about early language acquisition, little is known about the *minimum* environmental requirements for this process. There is, however, a strong body of opinion that language acquisition is a very robust function and the variance attributable to different levels of 'stimulation' may be quite small [4]

(4) 'Speech delay' is a symptom calling for differential diagnosis Some children with delayed speech development turn out to have a true language disorder, but the differential diagnosis from 'simple' speech delay can be very difficult in a young child.

(5) A child from a poor or potentially abusive family may be less able to reveal his full repertoire of language skills when attending a day care facility or when faced with the unfamiliar situation of a developmental assessment

(6) It is unwise to assume that two developmental assessments separated by a period should give identical quotients Substantial changes in scores in either direction are commonplace and must not automatically be attributed to environmental changes.

In clear cut cases of child abuse the presence of 'speech delay' may be of only marginal importance When care proceedings are brought on less solid evidence, evidence on the quality of *parental care* is highly relevant, but the deduction that parental care is likely to be inadequate *because* the child shows 'speech delay' deserves to be treated with considerable caution by the courts. If such evidence is to be presented a thorough multidisciplinary review is essential

References

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[2] Wells G Language variation In Fletcher P, Gorman M, eds *Language acquisition, studies in first language development* 2nd ed Cambridge Cambridge University Press, 1986

[3] Pennington BF, Smith SD Genetic influences on learning disabilities and speech and language disorders *Child Dev* 1983,**54**:369–87

[4] Wanner E, Gleitman LR, eds *Language acquisition, the state of the art* New York Cambridge University Press, 1982

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P Fletcher
Reading University

Apnoea monitoring and cot deaths

Sir,

The final conclusion in the report on apnoea monitoring,[1] 'apnoea monitoring has a place in highly selected situations', is more positive than previous articles but remains guarded. It would seem timely to attempt to redress this pessimistic approach Experience over the past five years has shown that the loan of Graseby MR 10 monitors to 85 families (25 machines are available, bought almost exclusively from voluntary donations) has been successful and rewarding With regular supervision at hospital paediatric clinics and by health visitors, the problems described by previous authors have not been seen. The monitors are reliable (only eight have been returned for servicing) and the number of false alarms diminish to negligible numbers after the first fortnight Occasional alarms when the infant's breathing is very shallow are reassuring as they indicate that the monitor is functioning

This service has been a demanding but not a formidable undertaking The gratifying effects on parental anxiety, sleep patterns, and fostering confidence in their infants have been a remarkably positive aspect of the counselling and support system developed in Leicestershire There have been no deaths on monitors but two parents are convinced that without monitors their infants would have died

In the light of such experience it seems unfortunate that the authors of the paper on a comparison between apnoea monitoring on weighing scales[2] indulge in highly subjective interpretations of the results For example, they found that 11% fewer symptoms in the infants were described by parents using apnoea monitoring as compared with weighing scales. Their interpretation was that babies on monitors are 'less closely observed and this could represent a hazard' An equally valid interpretation would be that the parents using monitors were less pathologically anxious about their babies than about infants being weighed daily This view is supported by the fact that monitors readily promoted reassurance in the immediate postnatal period, whereas weighing took some time to be accepted No assessment was made in the study of parental night time anxiety, touching their sleeping infants and sleeping habits—it is when a baby sleeps that anxiety levels are highest.

The report emphasises the fact that parents become 'over reliant' and 'more than 50% showed reluctance' to give up monitors. Scales, however, showed an 'advantage in the relative ease with which the tailing off process' could be achieved. Perhaps parents actually preferred the continuing confidence in a monitor—because they know cot deaths occur after 6 months—whereas they readily gave up the difficult and tedious daily weighing procedure.

The report includes a single case report that has been anecdotally quoted in cot death meetings as though it proves that monitoring does not save lives. The case illustrates insensitivity in the conduct of the study—the monitor alarmed very frequently, it was taken away from the baby at 28 weeks and, although the baby had been weighed regularly, a falling weight pattern was not recognised until after the baby had died at 32 weeks. This description suggests that the monitoring aspect of the study was not organised for the primary purpose of supporting parents and at risk infants nor for investigating babies who showed aberrations from normal progress.

The study revealed an expected and worthwhile result—parents are helped most by committed professionals who devote time and caring expertise to their anxieties. The study was not able to show that of the two technical modalities of monitoring, apnoea machines were in any way less successful. One message from the study is that more paediatricians (with help from family doctors, health visitors, and parent groups) should provide expert support services, including apnoea monitors, to those families who have suffered cot deaths.

References

[1] Foundation for the Study of Infant Deaths and the British Paediatric Respiratory Group. Apnoea monitors and sudden infant death. *Arch Dis Child* 1985;**60**:76–80.

[2] Emery JL, Waite AJ, Carpenter RG, Limerick SR, Blake D. Apnoea monitors compared with weighing scales for siblings after cot death. *Arch Dis Child* 1985;**60**:1055–60.

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Drs Emery, Waite, Limerick, and Carpenter comment:

We had objective evidence that indicated that both groups of children had equal morbidity. The apparent lower numbers of symptoms observed by the parents with monitored children could have several explanations, but the one that we passed on came from unsolicited comments of health visitors who had observed the parents' handling of the children in their own homes. Swift writes of 'the difficult and tedious daily weighing procedures'. May be he has some evidence about this, but in the anonymous reports from parents at the end of the surveillance not one parent has made such a comment.

To date our surveillance study has included 300 siblings of cot deaths. Four of these have died; all had been using monitors. Two died while on the monitors and the other two had monitors but were not on them at the time of death. We have had no deaths in the babies on scales alone. These numbers are of no significance but convince us of the need to continue our studies.

Does Swift believe that two of his 85 children have been saved by the monitors because the mothers believed so? The risk of cot death in a sibling is about one in 200. To prove that apnoea monitors or any other product prevent cot deaths would require a controlled study of a population of around 4000 siblings of cot deaths. At his current case load it would take Swift 116 years to prove the point that apnoea monitors could be saving a life.

In the United States a large number of paediatricians are providing apnoea and cardiac monitors and a recent attempt was made by a group in Los Angeles to evaluate their use in California.[1] They contacted all known monitor programme sites in the state and 30% of these with apnoea programmes and 40% of monitor vendors responded. The information evaluated 3406 infants—1841 having been on home monitors and 1565 not. The cot death rate for California was 1·6/1000 and for the babies on monitors it was 3·8/1000, with a similar rate for those not on monitors. Where there were technical problems with the home monitoring the death rate was 5·7/1000 births. There were 26 deaths in the children surveyed, of which four were due to non-accidental injury. In the California data there was no randomisation of care, thus with all these data the questions are still unanswered. Hence the need for our study.

Reference

[1] Davidson Ward SL, Keens TG, Chan LS, *et al*. Sudden infant death syndrome in infants evaluated by apnea programs in California. *Pediatrics* 1986;77:451–8.

The school entry medical examination

Sir,

I read with interest the article by Drs Whitmore and Bax on the school entry medical examination.[1] Despite the obvious attraction to the parents and teachers of having a doctor pronounce judgment on the normality or otherwise of the 5 year old starting school, the authors fail to make a convincing case for the routine school entry examination, and one must seriously question their continuation from both a scientific and cost effectiveness point of view.

Despite the authors' claim that many socially disadvantaged children do not receive 'satisfactory health surveillance' during their preschool years, there is little evidence to suggest that routine examinations detect health problems that are new findings—that is, were previously unknown and untreated—and/or important—that is, would make an appreciable impact on future health and functioning.

While I strongly support their assertion that clinical interpretation of a neurodevelopmental assessment is more valuable than a score, one cannot assume that other doctors have the same expertise as the authors. Variability in interpretation of results between different doctors might be expected.

The authors do not provide any information on how teachers and parents make use of their findings. Does an isolated finding on a neurodevelopmental examination provide information that is useful to a teacher in planning a teaching programme? It is well known that there is a wide range of normal maturation in this age group—a finding at one examination may be no longer present a few months later And what of a danger of labelling a child, so that a 5 year old who may be otherwise doing perfectly well is labelled as having a problem?

Finally, there are absolutely no data to suggest that an examination of this type makes any difference to outcome It would have to be shown that children who underwent such an examination at school entry would have an outcome that was better than children not so examined Such a study would be extremely difficult to undertake because of the multitude of other variables that effect functioning [2]

Given unlimited resources, one could perhaps support these examinations because they may provide reassurance to parents and teachers In most communities such a situation does not exist, and arguments could be made against them from a cost effectiveness point of view It seems more appropriate that nurses continue to be involved with children at school entry, but only to perform vision and hearing screening and to review health and developmental problems, perhaps with the aid of detailed health questionnaires completed by parents and consultation with teachers During the first year or two at school, teachers will certainly identify a further group of children who give rise to concern. The doctor would thus be available in a consultative capacity to assess those children identified by the nurse or teacher, or both, as having problems

While many would support the continued routine school entry examinations, there is precious little evidence that it is either a cost effective or valid method for reducing school problems In the face of diminishing resources it is essential to provide harder data to justify their existence

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[2] Oberklaid F The ritual school health examination An idea whose time has passed? *Aust Paediatr J* 1985,**21**:155–7

FRANK OBERKLAID
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Drs Bax and Whitmore comment

Dr Oberklaid's letter invites us to write another article! The purpose of our own article was to describe our present clinical method of conducting a school entrant medical examination and not to justify the procedure. We have referred to this in passing in other articles (including one by us to appear in *Dev Med Child Neurol* soon).[1 2]

Briefly, to take up some of Dr Oberklaid's points.

(1) We have good evidence that our routine examinations detected health problems that were not known about in the preschool health service: 94% of children whom we discovered had problems had not seen their general practitioner for those problems within the last 12 months and a third of the children we examined had no available preschool health notes; of those for whom notes were available, two out of five had not been seen since the age of 2.

(2) We do not see why the school health service should aim to employ doctors who are less competent than our aged selves

(3) In the past teachers have often received dribs and drabs of information from doctors outside school, which are confusing to them It is indeed our practice to discuss in detail our findings with the teacher and to discuss and explain to them the importance of findings. Our examination aims to report on the present developmental state of the child and we are extremely cautious in talking to teachers about drawing any implications for the future Nevertheless, our neurodevelopmental examination has proved extremely robust in making predictions, as our own data suggests (see our article to be published in *Dev Med Child Neurol*) and that of other workers who have used our scheme.[3]

(4) It is quite true that we are bad at treating many forms of neurodevelopmental disorder from cerebral palsy to learning disorders There seems to be a new philosophy abroad that you do not diagnose unless you can treat; we believe that this is alien to the whole history of medicine

(5) We are not businessmen and we are bad at deciding whether things are cost effective We are dismayed though with the fact that community paediatrics is constantly taking the brunt of the cost effective attack and we wonder if the businessmen involved would devote more time to looking at some of the things that go on in hospital and general practice

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Oedema and the aging prima donna

Sir,

It may be a case of the aging prima donna but I was a little disappointed to find that Cartlidge and Rutter in their paper on serum albumin and oedema[1] made no reference to our studies in this field [2–4] It is of course disappointing to have published work overlooked However (and perhaps this is the only justification for this letter), our studies included a wide range of measurements of plasma proteins, albumin, and (directly measured) colloid osmotic pressure that might have made useful data for comparative discussion with the Nottingham data Most particularly I would have been interested to hear their discussion of our apparent findings of a complex relation between plasma proteins, albumin, and colloid osmotic pressure For all this I do not have any quarrel with the conclusion of their paper that the interpretation and treatment of measurements of plasma proteins in the preterm infant is greatly overrated, and I think that Cartlidge and Rutter have done paediatrics a service in drawing attention to the curiously large scatter of plasma proteins concentrations in preterm and newborn infants.

J D Baum
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Drs Cartlidge and Rutter comment·

We were sorry to discover that Professor Baum has carried out so much work in the field of neonatal oedema to which we made no reference This was no intended slight (we were unaware of his work), but his disappointment is understandable When we set out to perform the study we carried out a search of the published works through *Index Medicus,* using the preterm infant, oedema, and albumin as key words, and choosing papers that seemed relevant by their titles We knew of the study from 1971 on colloid osmotic pressure in the fetus and newborn infant,[2] but as it contains no data on albumin concentrations or oedema in preterm infants we did not refer to it The study on colloid osmotic pressure in erythroblastosis fetalis does contain data on albumin concentrations in preterm infants but the title gives no clue to this [3] The most important reference, the monograph 'Oedema in the newborn,[4] certainly contains a lot of information on oedema and albumin concentrations in the preterm infant, some of which we have duplicated. It does not appear in *Index Medicus,* however. and is not referred to in any article that we have come across. We regret that we were unaware of it, but the exponential rise in the volume of medical publications (to which these letters will contribute!) makes such rediscovery of the wheel more likely.

We have since read and enjoyed 'Oedema in the newborn.'[4] The chapter on oedema in the preterm infant provides data on cord albumin concentrations at different gestational ages from 33 weeks onwards. Our values are somewhat lower, perhaps because they were all obtained after birth, but show a similarly large scatter—our findings on infants below 33 weeks' gestation further emphasise the important influence of gestation on serum albumin Baum suggests that oedema in preterm infants is not looked for now compared with the earlier days of neonatology, except in very immature infants Our data strongly supports this We do not know why very immature infants develop oedema—it does not seem to relate to illness or serum albumin. Clearly, we have both shown that subcutaneous oedema is not simply due to a low colloid osmotic pressure produced by a low serum albumin concentration Baum has found that levels of colloid osmotic pressure in preterm infants without oedema are often below 20 cm of water, levels that would produce generalised oedema in a child with the nephrotic syndrome. Perhaps the low mean arterial pressure of the preterm infant results in a low hydrostatic pressure and therefore protects against severe oedema Whatever the reasons are for oedema, the message seems to be that hypoalbuminaemia of prematurity is a usual finding, not a disorder that needs treatment.

References

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Cystic fibrosis and diabetes mellitus

Sir,

Cystic fibrosis is associated not only with chronic suppurative lung disease and exocrine pancreatic insufficiency but also with endocrine dysfunction of the pancreas, leading to impaired glucose tolerance, decreased insulin production and diabetes mellitus in some children [1] Measurement of glycosylated haemoglobin (HbA_{1c}) has been shown to be useful for assessment of children with impaired glucose tolerance.

We measured stable HbA_{1c} concentrations by a modification of the Corning electrophoresis method[2] in 21 children with cystic fibrosis, aged 1–16 years, regularly attending our clinic, and in 50 normal children, aged 1–16 years. Three of the children with cystic fibrosis were receiving insulin for clinical diabetes mellitus The mean (SD) HbA_{1c} concentration in the remaining 18 children was 8·1 (1·5)% (range 6·0–11·3%) compared with 6·0 (0·8)% (range 4·3–7·7%) in the normal group ($p<0·001$). All of the children with cystic fibrosis had HbA_{1c} concentrations equal to or greater than the mean of the normal group and in 55% the HbA_{1c} concentrations were more than two standard deviations greater than the normal group mean

The degree of glucose intolerance may be relevant to morbidity and problems of growth in children with cystic fibrosis and requires further study. Treatment with prednisone has been shown to improve pulmonary function in such children,[3] and although that study detected no change in HbA_{1c} concentrations, careful monitoring of glucose tolerance would seem to be indicated if this treatment is begun.

We suggest that HbA_{1c} concentrations will be of value for monitoring children with cystic fibrosis and if repeated at six to 12 month intervals would indicate any progressive impairment of glucose tolerance. This would allow earlier detection and treatment of associated diabetes mellitus

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Alternate-day prednisone reduces morbidity and improves pulmonary function in cystic fibrosis *Lancet* 1985,ii 686–8.

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Spermatic cord torsion

Sir,

In his recent annotation Matthews raises a number of points that require correction.[1] The statement that neonatal spermatic cord torsion occurs 'especially in the premature baby' is not borne out by any other authors on the topic, and, in fact, in 62 patients in the published reports for whom information is available the mean birth weight was 3600 g In fact, this condition seems to be confined to term babies and, indeed, in general to large term babies While I agree that surgery to fix the contralateral testis is mandatory in these infants, urgent surgery to attempt detorsion of the twisted testis is not necessary in most instances as the testis is almost invariably beyond salvage In 25 instances in the published reports where detorsion and retention of the testis was performed there were only two occasions where testicular survival was thought to have occurred (Burge DM. Neonatal testicular torsion and infarction. aetiology and management Unpublished data.)

The comment that idiopathic scrotal oedema is a rare condition is slightly misleading. Of the children referred to this unit from the Southampton district in the years 1980–85, there were 46 children with testicular torsion, 22 children with torsion of hydatid of Morgagni, and 31 with idiopathic scrotal oedema Other authors have noted that this condition is probably the second commonest cause of acute scrotal disease that leads to admission to hospital [2] Considerable experience in making this diagnosis is required, however, before conservative management is adopted

I wholeheartedly agree with the comments made regarding epididymo-orchitis and the worrying frequency with which this extremely rare condition in the paediatric age group is still being diagnosed by referring practitioners. The medical school teaching that all acute scrotal disease requires surgical exploration is still by far the safest starting point in the management of a child with scrotal pain

References

[1] Matthews PN Spermatic cord torsion *Arch Dis Child* 1986,**61**:426–7

[2] Brereton RJ, Manley S Acute scrotal pathology in boys *Z Kinderchir* 1980,**29**:343–57

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Dr Matthews comments

Thank you for correctly pointing out that neonatal spermatic cord torsion usually occurs in the full term baby I still believe that urgent surgery offers the best chance of testicular salvage and although I concede that more babies will be lost than saved, there is nothing to be gained by delay, and with more widespread adoption of an urgent surgery policy maybe we could improve on the rather dismal testicular salvage rates in the neonate

I agree that idiopathic scrotal oedema is more common that was originally thought but felt that non-diagnosis of this strange condition was preferable to wrongly diagnosed testicular torsion

Cost of Stycar boxes

Sir,

I was extremely surprised to find that the Stycar Vision and Hearing test equipment cost £95·00 and £59·95, respectively These boxes consist of a few toys, rattles, polystyrene balls, and standard cards for vision and hearing checks.

The rattles break often and the toys go missing frequently, and I am sure it is a very profitable business for the manufacturers

I hope all of us who use Stycar boxes realise their cost and ask ourselves and the manufacturers why they cost so much

A Thenabadu
New Malden,
Surrey

Mr M Jackson comments·

We are grateful to Dr Thenabadu in raising this question but are rather upset at the suggestion that Stycar offers only 'a few toys, rattles, etc'

The Stycar series of tests, Hearing, Vision and Language, have, of course, proved of immense value to practitioners over the years in helping them to obtain reliable information about children's capacity in hearing comprehension and visual comprehension and acuity and their ability to comprehend and express themselves in the spoken language

The components and style of packaging have been those that suited the needs of practitioners but it is perhaps important that over the last 12 months or so a slightly different pattern of requests has begun to emerge and we have recently been in touch with many paediatricians and medical officers to identify if a repackaging is required The current 'make up' of the Stycar tests and style of packaging is certainly not cheap—partly because several of the items need to be especially prepared and in such small quantities that high costs are inevitable

If we are able to identify accurately alternative and more economic means of presentation then we will be only too happy to examine them because, ironically enough and in direct contradiction to what Dr Thenabadu suggests, the present format of these tests is most certainly not profitable to us

NFER-Nelson do operate responsibly and we fully appreciate that there are probably many 'costs' and other factors that may not be obvious or apparent to our customers We would have been happy to talk these through with Dr Thenabadu if she had contacted us and would certainly be pleased to hear how she uses the test items in day to day practice It is important also to mention that NFER-Nelson are currently undertaking a major new product aimed at providing practitioners with a totally new developmental screening procedure for the 0–5 year olds based on the Stycar Sequences It has been in the course of our widespread discussion of this that so much useful new information has come back to us concerning the current usage of the existing Stycar tests

Vision testing beads

Sir,

I wish to report a simple device for screening the visual acuity of children over 6 months old The device itself is constructed from four spherical white beads (approximately 2 mm, 3 mm, 6 mm, and 12 mm in diameter) that are strung between two small spools on a 70 cm length of dark 3/0 monofilament thread (Figure) When not in use, the device can be stored in a small container, with the thread being wound onto one or other spool to prevent tangling

While sitting facing the child, the clinician palms one spool in each hand, stretching the thread taut and roughly horizontal just in front of a dark background (such as an upright black attaché case on the clinician's lap) All but one bead is trapped against the spools, and the remaining bead is shuttled back and forth by raising first one and then the other hand The child's visual acuity can be assessed from how small a bead elicits visual tracking when the beads are 3 metres (or 1·5 metres) away.

For children aged 18 months or over, the clinician's clothing or case can provide a suitable dark background Children under the age of 18 months generally find the clinician's face more interesting than the shuttling bead This problem can be overcome by using a small screen with an eye slit mounted on the lap

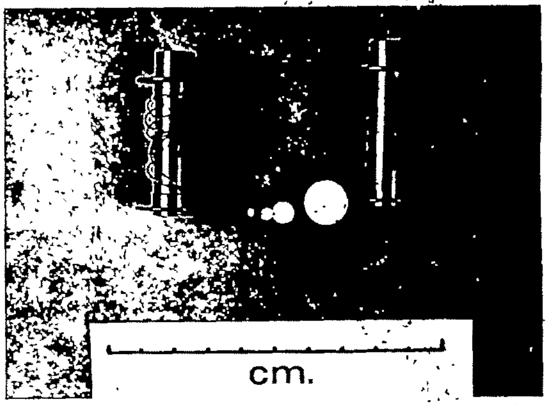

Figure *Close up of vision testing beads*

Preliminary field trials indicate that Sheridan's norms[1] for the Stycar graded balls can be transferred to sliding beads: the normal 6 month infant can track a 6 mm bead at 3 metres (or a 3 mm bead at 1 5 metres), and from 8 months of age upwards normal children can track a 3 mm bead (and often a 2 mm bead) at 3 metres

The vision testing beads are cheap, compact, and easy to make and use They have some advantages over the standard Stycar techniques no need for a room large enough to accommodate a long black mat (unlike the Stycar 'rolling balls' technique) and no need for a large screen and a room with one black wall (unlike the Stycar 'mounted balls technique')

Reference

[1] Sheridan MD The Stycar graded-balls vision test *Dev Med Child Neurol* 1973,15:423–32

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Archives of Disease in Childhood, 1987, **62,** 104–105

Book reviews

Textbook of Neonatology. Edited by N R C Roberton Pp 907. £90 00 hardback. Churchill Livingstone, 1986

Do not confuse this book with Dr Roberton's pocket manual of neonatal intensive care; this one is a large multi-author work on the newborn that compares favourably with the big American books, such as Shaffer's 'Disease of the newborn' or G Avery's 'Neonatology'. Without wishing to appear chauvinistic, at last we have a major British book covering the whole of neonatal paediatrics as practised in this country. At least it's mainly British, with 42 of the 62 contributors coming from the United Kingdom, only 12 from North America, with four from Australia and four from mainland Europe Although I have a high regard for American neonatology I found Dr Roberton's book far more relevant to our own beliefs and practices

The first of the books' eight sections has five chapters on general aspects of neonatology, such as epidemiology, psychology, ethics, follow up, and death The next section is on obstetrics for the neonatologist and section three deals briefly with embryology and fetal growth General neonatal care in section four covers examination of the newborn, temperature control, all types of feeding, pharmacology, and resuscitation There then follows the main body of the book in section five with 14 chapters on all aspects of disorders of the newborn described mainly by organ systems

Some chapters such as the one on neurological disorders, are further subdivided into as many as eight parts This section is comprehensive and well balanced, mainly relating to everyday clinical practice but also providing useful reference to the less common disorders. The remainder deals with organisation, procedures, and the usual appendices of normal values, etc The book is produced to a high standard with clear layout, many subheadings, tables, and diagrams There are plenty of black and white photos and some in colour The *x* rays and ultrasound scans, which so often come out poorly in print, have reproduced well. Each chapter has a sizeable list of references. At £90 it may be beyond the pocket of many junior staff, but I can certainly recommend it to all paediatricians working with the newborn, and I am sure every neonatal unit should have a copy.

BRIAN SPIEDEL

Respiratory Disorders in the Newborn. Current Reviews in Paediatrics. By V Y H Yu Pp 156· £19·00 hardback Churchill Livingstone, 1986.

This excellent book is the latest in the series 'Current reviews in paediatrics' under the overall editorship of Dr Tim Chambers and Professor A Green

The single author format allows the very complex subject of respiratory disorders in the newborn to be covered in a small but detailed book with appropriate cross references and very little repetition Each subject is covered in a short, concise, but very clear description, usually covering what is known of predisposing factors, pathophysiology, and prevention as well as acute and chronic management and long term outcome Each section is extremely well referenced and in general the author manages to define clearly those statements that are based on objective studies or published data from those statements that reflect his own considerable clinical experience but may not yet have been subjected to detailed scientific scrutiny

The descriptions of anatomic and physiologic development of the lung and the respiratory system in general are short enough to be read by the interested resident in neonatal medicine but detailed enough and sufficiently well referenced to provide an appropriate guide to further reading There follow sections on perinatal asphyxia, aspiration syndrome, hyaline membrane disease, pneumonia, pulmonary oedema, pulmonary air leak, pulmonary hypertension, chronic lung disorders, apnoeic attacks, and congenital anomalies of the respiratory system In each of these chapters the same format is followed with an extraordinary amount of information being crammed into very concise descriptions of the various conditions being covered As for the sections on physiology and anatomy, all the clinical sections are extremely well referenced and the reader is left in no doubt about which aspects of care are standard and widely applied and which are perhaps slightly more idiosyncratic

If there is any real criticism of this book it is that relatively little attention is given to experimental or unconventional approaches to management, which might be of value to the audience for whom this book is intended as it is often helpful to know which alternative approaches have been tried and what results, if any, are available.

In summary, this book should prove of great value to both medical and nursing staff involved in the care of newborn infants It is concise enough to be read throughout by the more highly motivated residents but is detailed enough to provide a useful reference book and as such find a place on the shelves of most special and intensive care baby units

P J FLEMING

Care of the Child with Diabetes. Edited by J D Baum and A L Kinmouth Pp 228 £24·00 hardback Churchill Livingstone, 1986

This sets out to be 'both a text book and a practical manual of diabetic care' It succeeds better as a textbook. In its success, however, it shows a highly professional multidisciplinary approach, an exemplary model for paediatric diabetic care in the 1980s Anyone having the care of diabetic children should consult a copy, and that includes parents. Can we hope that in the second edition the patient's voice will be heard verbatim and not only through his parents?

J H KEEN

Standards in Pediatric Orthopedics. Tables, Charts and Graphs Illustrating Growth. Edited by Robert N Hensinger Pp 403 $65·50 hardback Raven Press, 1986

This is a book of graphs, tables, and diagrams covering a wide range of aspects of growth from the fetus to the fully grown It is designed primarily for those interested in paediatric orthopaedics, as the title implies, and has sections on spine and skull, hip and pelvis, upper extremity, hand, lower extremity, and foot These include comprehensive data on bone sizes, shapes, changes, and relations There are also chapters on gait, biomechanics, growth, and maturation in more general terms, including puberty and neuromuscular function This last comprises mental development as well as physiological development of strength and skill This is a massive compilation of over 400 high quality illustrations but with the minimum of description. The material is mostly presented directly from original publications of many authors and is as up to date as possible.

When I first opened this book I expected to find it invaluable Sadly, this did not prove to be the case The number of contributions is so great that on any particular subject it is difficult to know which one to select, and the lack of textual description makes many areas difficult for the non-orthopaedic specialist to understand Inevitably, there is little consistency in the format as the material comes directly from so many sources There is little to which I, as a paediatrician with a special interest in growth, would have cause to refer The last chapter is useful, including such familiar data as Apgar, Dubowitz, Bailey, and Denver scoring There are also occasional invaluable oddments within the book, such as standards for growth of children with achondroplasia and other bone dysplasias and performance standards of strength and skill of growing children There are excellent illustrations of normal gait, and the abnormal progression in Duchenne dystrophy Though much of the rest is of interest, however, there is little of direct clinical application. Of course, not being American, I found the lack of reference to non-American standards disappointing In this massive accumulation of data I found only one group derived from Tanner This was the velocity standards for height and weight Yet the distance standards for all body measurements, the criteria for pubertal rating, skeletal age assessment methods, prediction of adult height, etc, included few of those with which we in Europe are familiar and accept as appropriate

Of course, this book has not been written for the British paediatrician! For those for whom it is primarily intended, American orthopaedic surgeons, it may be excellent, but I am in awe of their understanding of such a complex specialty

J M H BUCKLER

Malformation in Children from One to Seven Years. A report from the collaborative perinatal project By N C Myrianthopoulos. Pp 250· £55·00 hardback. Alan R Liss Inc, 1986.

This is a study of 47 775 singletons who were followed through the ages of 1 to 7 years to describe the types and frequencies of major and minor malformations observed during that period The malformations are analysed by system, single, and multiple malformations and by race and sex. There is so much information here it is a bit like being asked to review a telephone directory Impressive and indispensable for those really interested in the subject, but dispensable for most paediatricians

R M WINTER

The Problem Knee—Diagnosis and Management in the Younger Patient. By M F Macnicol Pp 184. £19·50 hardback Heinemann, 1986.

The author has aimed his book at a wide readership, which includes physiotherapists, coaches, family doctors, and accident officers He has emphasised the importance of accurate diagnosis and given general guidance on operative treatment With the number of books already available on the knee it seemed at first sight unlikely that there was a place for yet another one. By the clear definition of his objectives and emphasis on overall management, however, Mr Macnicol has produced an interesting and useful short book It provides up to date information on the present day treatment of common problems in the knee There is a systematic description starting from mechanisms and presentation of injuries to techniques involved in the rehabilitation of the damaged knee The section on the diagnosis of the various ligamentous injuries is particularly clear and well illustrated. Methods of investigation are discussed in some detail and include examples of computed axial tomography and images produced with nuclear magnetic resonance Although the main bulk of the text is devoted to injuries, there is a useful chapter on non-traumatic conditions.

There is no doubt that this book fills a gap. It is very likely to be popular with orthopaedic residents and registrars as well as the audience for which it is intended.

LESLIE KLENERMAN

Cranial Computed Tomography in Infants and Children. By E N Faerber Pp 237. £16 00 hardback. Blackwell Scientific, 1986

This book is not solely an atlas of cranial computed tomography, there is a good deal of explanatory text Scanning techniques are clearly described and the section on normal anatomy is excellent The book is comprehensive, sometimes at the expense of detail on the more common conditions The majority of illustrations are clear, but some are far too dark to see any detail On the whole I found this book a very useful guide It is well indexed and the references are up to date

S H GREEN

Archives of Disease in Childhood, 1987, **62,** 106

Meetings in 1987

British Society of Paediatric Gastroenterology
9 January, London
Further details: Dr M J Brueton and Dr B Sandhu, Department of Child Health, Westminster Children's Hospital, Vincent Square, London SW1P 2NS

Neonatal Society
26 February, London
3 July, Manchester
5 November, London (provisional)
Further details: Dr J K Stothers, Department of Physiology, London Hospital Medical College, Turner Street, London E1 2AD

Paediatric Research Society
27–28 March, Brighton
Further details: Dr G S Clayden, Paediatric Research Laboratory, Rayne Institute, St Thomas' Hospital, London SE1 7EH

Clinical Genetics Society
2–3 April, Leicester
Further details: Professor N C Nevin, Department of Medical Genetics, Institute of Clinical Science, Grosvenor Road, Belfast BT12 6BJ, Northern Ireland

British Paediatric Association—59th Annual Meeting
7–10 April, York
Further details: British Paediatric Association, 5 St Andrews Place, Regent's Park, London NW1 4LB

European Association Meeting, Child Abuse and Neglect
6–10 April, Rhodes, Greece
Further details: Dr M Lynch, Newcomen Centre, Guy's Hospital, St Thomas' Street, London SE1 9RT

European Society for Paediatric Gastroenterology and Nutrition
24–26 June, Lisbon (provisional)
Further details: Professor S De Sousa, Department of Paediatrics, Hospital de Santa Maria, Avenue Egas Moniz, 1600 Lisbon, Portugal

British Association for Perinatal Paediatrics
9–11 July, Nottingham
Further details: Dr D Curnock, City Hospital, Nottingham NG5 1PB

European Paediatric Respiratory Society
25–28 August, Helsinki, Finland
Further details EPRS Meeting 1987, Congress Secretariat, c/o Finnish Anti-Tuberculosis Association, Kalevankatu 9, 00100 Helsinki, Finland

European Society for Paediatric Nephrology
3–5 September, Budapest
Further details: Professor D Boda, Department of Pediatrics, University Medical School, 18 Korányi Fasor, H-6725 Szeged, Hungary

European Society for Pediatric Research
6–10 September, Padova
Further details: Professor F F Rubaltelli, Università degli Studi di Padova, Istituto di Clinica Pediatrica, Via Giustiniani 3, 1-13500 Padova, Italy

European Society for Paediatric Endocrinology
7–8 September, Toulouse, France
Further details: Professor A Aynsley-Green, Department of Child Health, The Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH

British Paediatric Respiratory Group
18–19 September, London
Further details: Dr A Greenough, Paediatric Department, King's College Hospital, Denmark Hill, London SE5 9RS

Paediatric Research Society
18–19 September, Cardiff
Further details: Dr G S Clayden

British Society of Allergy and Clinical Immunology
October, London
Further details: Dr J O Warner, Brompton Hospital, Fulham Road, London SW3 6HP

Archives of Disease in Childhood, 1987, **62**, 107–108

Instructions to authors

Papers for publication should be sent to the Editors, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR

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These should usually conform to the conventional structure of summary, introduction, methods, results, discussion, and references. The title should occupy no more than two lines of the title page (8 to 10 words) and should not contain the words 'child', 'children', or 'childhood' (already implicit in the title of the journal). The summary should be no longer than 150 words and should set out what was done and the main findings and their implications.

Short reports

Short papers, brief laboratory observations, and preliminary communications should be submitted for this section (single case reports will usually be considered in this form only). Length must not exceed two printed pages of text. In general this will be less than 900 words, including a summary of less than 50 words, one or two small tables *or* illustrations and up to 6 references. An abbreviated title of no more than 38 characters is required for the title page A report of a negative result trial, based on a reasonable hypothesis, is more likely to gain acceptance if submitted as a *very* short report of less than 500 words.

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Drugs should be given their approved, not proprietary names, and the source of any new or experimental preparations should be given. Abbreviations should not be used. Scientific measurements should be given in SI units: conversion factors to traditional units should also be supplied. Blood pressure, however, should be expressed in mmHg and haemoglobin in g/l.

Any statistical method used should be detailed in the methods section of the paper and any not in common use should be either described in detail or supported by references Previously published procedures and techniques need only a reference to the original Tables and illustrations should be submitted separately from the text of the paper, and legends to illustrations should also be typed on a separate sheet Tables should be simple and should not duplicate information in the text of the article, they should be numbered and be comprehensible to the reader without the text.

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Most articles do not require more than 20 references and many need substantially less. References should be numbered in the order in which they appear in the text At the end of the article the full list of references should give the names and initials of all authors (unless there are more than six, when only the first three should be given, followed by *et al*). The authors' names are followed by the title of the article, the title of the journal abbreviated according to the style of *Index Medicus* (see the January issue of *Index Medicus*); the year of publication, the volume number; and the first and last page numbers. Titles of books should be followed by place of publication, publisher, and year.

1 Barson AJ, Tasker M, Lieberman BA, Hillier VF Impact of improved perinatal care on the causes of death. *Arch Dis Child* 1984;**59:** 199–206.
2 Dowling S. *Health for a change.* London: Child Poverty Action Group, 1983.

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References

[1] International Committee of Medical Journal Editors, Uniform requirements for manuscripts submitted to biomedical journals *Br Med J* 1982,**284:**1766–70
[2] Anonymous Research involving children—ethics, the law, and the climate of opinion [Editorial] *Arch Dis Child* 1978,**53.** 441–2

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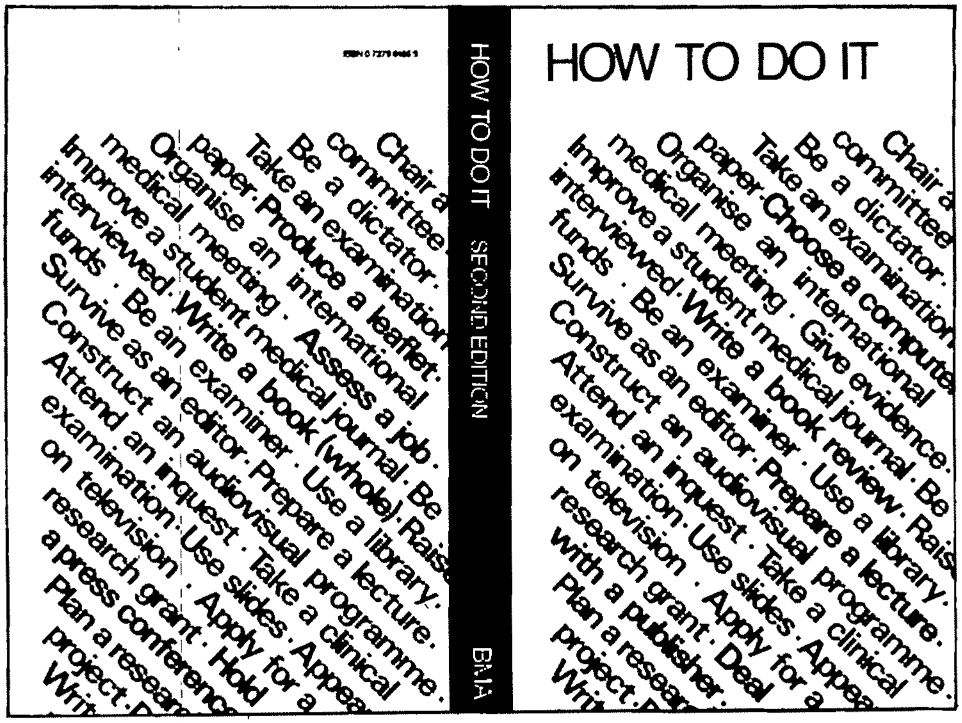

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An International Journal

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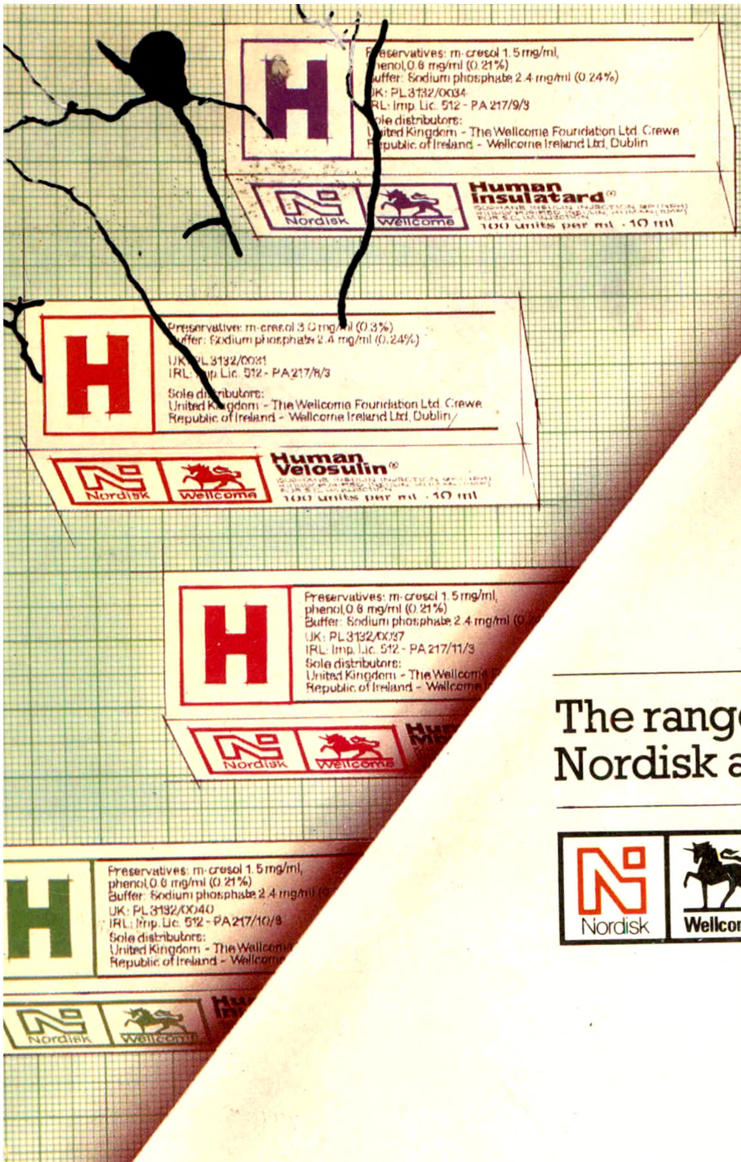
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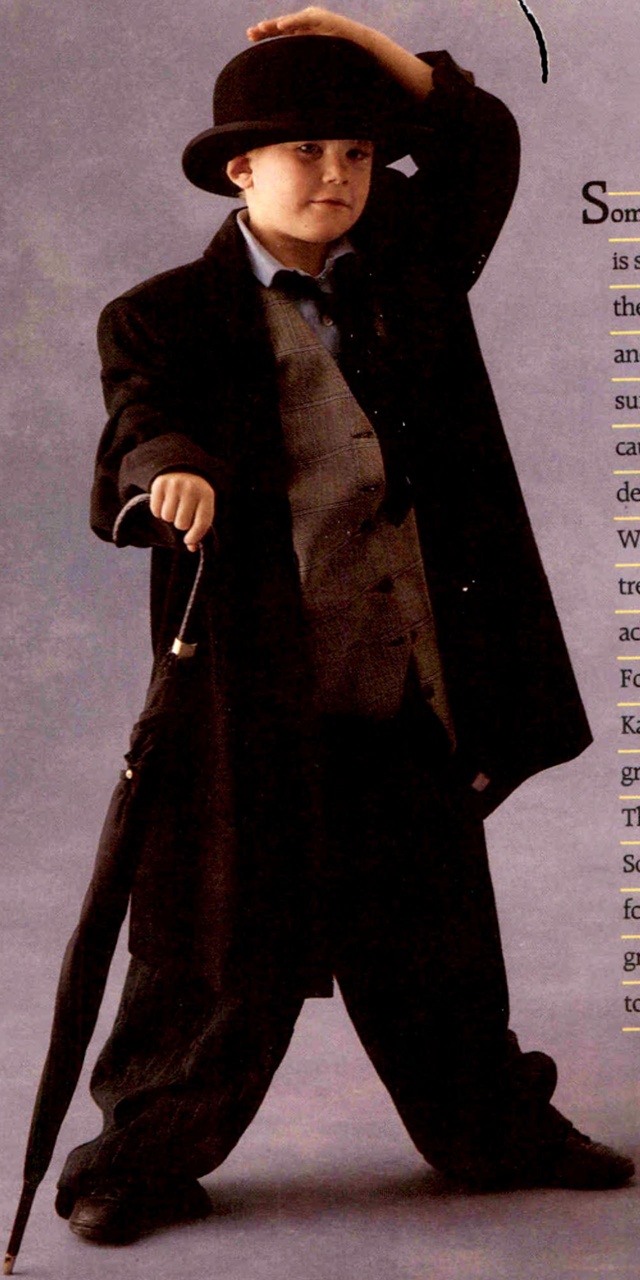

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Annotations

Malformations in different ethnic groups

Depressingly little is known about the cause of malformations. Despite a history dating back to antiquity and an incidence approaching one in 30, over 50% of major congenital malformations, defined as those that seriously interfere with viability or physical well being, are unexplained. Thus any approach that may shed light on an area of such shameful medical ignorance is to be welcomed The study of ethnic differences is one such approach.

Pitfalls and limitations

It is worth considering in some detail the problems confronting the epidemiologist wishing to explore this area, for they are formidable.

Definition. At the outset it will be necessary to define exactly what is meant by a malformation, which may be 'intrinsic', inferring that the organ was programmed to be abnormal, or 'extrinsic', resulting from damage by an external agent such as a drug or virus. Many surveys have also included 'deformations', such as talipes, and problems arise in trying to classify conditions such as congenital dislocation of the hip, which may be neurogenic in origin or arise from interaction between a genetic predisposition and an adverse environment. It will also be necessary to decide whether to include relatively trivial malformations, such as polydactyly, which is particularly common in babies of African origin.[1] A useful starting point in any such survey will be reference to the recently published recommendations of an international working party.[2]

Ascertainment. This should be unbiased, accurate, and full. Relying on forms completed by clerical officers or tired junior medical staff is of dubious value. Every diagnosis should be confirmed, an exercise that in many cases will involve recourse to expert opinion. Ideally, ascertainment should be as close as possible to complete in a well defined, and preferably stable, population rather than in a high risk maternity unit. Thus provision should be made for including the malformed stillbirths and babies born at home or in outlying small maternity units. Finally, consideration will have to be given to the ascertainment of infants with late presenting malformations.

Confounding variables. These are numerous. When comparing ethnic differences in incidence within a large community allowance will have to be made for differences in antenatal care, diet, maternal age and parity, social class, and occupation. These points are illustrated by a study from Leicestershire, which indicated that the relative risk for perinatal mortality due to congenital malformations was greater if the general practitioner was not on the obstetric list than for an Asian versus non-Asian mother.[3]

Implications. Care should be given to the possible consequences of identifying ethnic differences that may be attributable to cultural or religious practices. Attempts to introduce widespread sickle cell screening in the black population of North America were a disaster, and efforts to introduce screening for cystic fibrosis carrier detection in whites might be no more successful. If it should transpire that the administration of surma or the practice of consanguinity were disadvantageous this information would have to be handled with great sensitivity. In the author's experience many Muslims do not accept that consanguinity is deleterious, and if proven it would not be easy to convey these sentiments while at the same time retaining the confidence of that community.

Genetic or environmental?

Given this long list of preconditions, what can anyone realistically hope to achieve? Much energy has been invested for relatively little return, but fortunately some useful information has emerged. Establishing the cause of a malformation is a first vital step towards primary prevention.

Genetic. At one end of the aetiological spectrum careful family studies and pedigree analysis have revealed that some anomalies are entirely genetic in origin. Examples include the hydrolethalus syndrome characterised by hydrocephalus, polydactyly, and early lethality.[4] This disorder shows autosomal recessive inheritance and is observed almost exclusively in Finland, presumably as a result of a founder effect in a relatively small and geographically isolated community. The study of such a rare disorder in a particular community enables its genetic aetiology to be established so that recurrence risks and prenatal diagnosis can be offered.

Environmental. At the other end of the spectrum some conditions such as Minamata disease have been found to be entirely environmental. In this disorder, damage to the developing brain occurs as a result of maternal or postnatal ingestion of organic mercury, either in polluted fish and shellfish as in the original Japanese outbreak[5] or as a result of grain having been treated with a fungicide containing methylmercury as occurred in Iraq.[6] Having confidently identified such a potent teratogen it should not be too difficult to persuade even the most intransigent government to act.

Genetic and environmental. Many of the more common single organ malformations fall somewhere in the middle of the aetiological spectrum and show so called 'multifactorial' inheritance, implying a polygenic predisposition plus environmental insult This is the case for neural tube defects and cleft lip (with or without palate), the geographical and racial distributions of which have been reviewed by Leck.[7] For cleft lip it was noted that ethnic differences (high in Mongoloids, intermediate in whites, and low in Negroids) persist after migration, suggesting that the variation is largely genetic with a relatively small environmental contribution. In contrast incidence differences in neural tube defects, which are pronounced both between and within ethnic groups, are influenced considerably by migration, pointing to a major environmental component.

Consanguinity—good or bad?

In several ethnic groups, particularly those originating from the Indian subcontinent, first cousin and uncle-niece marriages are encouraged. Given that most humans probably carry at least one deleterious recessive gene, a strong case could be made for discouraging consanguineous marriages, in which rare recessive genes are more likely to 'meet up with themselves' than in an outbreeding society. At an anecdotal level the author has been impressed by the risks attached to consanguineous marriages.

Anecdote has a scientific value of less than zero, however, and it has been suggested that in a community that has been practising consanguinity for many generations all of the bad genes will have been bred out. Thus any study of the incidence of malformations in different ethnic groups, consanguineous and non-consanguineous, would be of value. Circumstantial evidence in the United Kingdom does point to consanguinity being deleterious, with increased perinatal mortality due to congenital malformations having been noted in the Asian, and in particular Pakistani, communities of Bradford[8] and Birmingham.[9] Consanguinity would be expected to increase the incidence of rare recessives and to a lesser extent of multifactorial disorders, so that it is interesting to note that a study from Manchester and Leeds found a high incidence of the possibly multifactorial polysplenia/asplenia syndrome in Muslim Asian children whose parents were consanguineous.[10]

Confirmation of a suspected deleterious effect of consanguinity would be of value for two reasons. Firstly, it would provide a basis for a programme of public education that could be integrated into the existing link worker schemes and school teaching programmes,[11] but only with the agreement and support of local ethnic leaders Secondly, it would enable the genetic counsellor, when confronted by consanguineous parents with an abnormal child in whom no clear diagnosis can be made, to offer with confidence a recurrence risk of 25%, rather than a lower risk that might otherwise seem appropriate.

The future

There is clearly a need for well planned comprehensive and preferably prospective surveys of malformations in different ethnic groups sharing as far as possible the same environment. The study of individual malformations in different communities may help provide clues to aetiology, while the overall incidence of malformations may yield valuable information about the importance or otherwise of consanguinity, obstetric care, social circumstances, and other factors that may influence the embryonic milieu. The point has been made before, and is worthy of repetition, that the likelihood of discovering anything new in medicine is relatively small, but infinitesimal if no attempt is made.

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Club foot

Diagnosis of a club foot is easy. In contrast, it is the prognosis that is difficult and it is not a simple task for the surgeon to forecast accurately the outcome of treatment when the child is first seen. This reflects the problem of accurate measurement of the severity of the deformity, not only in static terms but also in relation to rigidity and degrees of stiffness. Lack of precision complicates the initial assessment and makes comparison between different methods of treatment and the reported results almost impossible.

Diagnosis

The first priority of examination is to establish whether there is a fixed structural deformity or a postural attitude that has resulted from the baby's position in utero. Severe deformity is associated with fixed equinus and varus of the heel, which is small and tucked up towards the medial malleolus, with a deep medial plantar crease and supination of the forefoot. A normal foot is supple and mobile and can readily be dorsiflexed, so that the dorsum comes into contact with the anterolateral aspect of the shin.

Early management

Of the variety of different techniques used for the early management of club feet, the use of adhesive strapping and repeated gentle manipulations, attributed to Robert Jones, is the most effective. It is cheap and easy and can be safely performed by physiotherapists who see the child two or three times a week. With the use of this method from birth, it is usually possible at 6 weeks to distinguish mild varieties of talipes likely to respond to conservative measures alone from those that will require surgery.

Surgical management

Early operation is an advantage as there is less time for the relatively soft bones of the developing foot to become deformed. Green and Lloyd Roberts found no significant difference, however, in the outcome of operations in children who were treated surgically up to 20 weeks, and for optimal results they regarded 14 weeks as their upper limit.[1]

There are two main surgical approaches, either to concentrate on the correction of the hindfoot as suggested by Attenborough,[2] and deal with forefoot problems if necessary at a later date, or to carry out a primary radical correction of the whole foot as advocated by Turco[3] and Clark and Silk.[4] Radical operations expose the foot to the hazard of joint stiffness and overcorrection. Attenborough's thesis is based on his observation that the fundamental abnormality is the fixed equinus deformity of the talus, which, even in a normal foot, gives rise to inversion of the subtalar joint and thus of the forefoot. He set out to correct the hindfoot only and found the forefoot usually followed at the same time, except for residual varus. A recent modification of the posterior approach, always carried out from the medial side, is to utilise a lateral incision as well, if necessary, or primarily in the less severe case to deal with soft tissue tethering in the region of the peroneal tendons.[6]

The more radical school base their operations on the observation that the essential abnormality of the club foot is the dislocation of the navicular and forefoot to the medial side of the talar neck. It is this displacement that they aim to correct by a 'pantalar' reduction.[5]

If full correction is not achieved early there are a number of additional, mainly soft tissue, procedures—for example, tibialis anterior tendon transfer—available to improve the foot before skeletal maturity, but, if all efforts fail, the child can then be certain of a plantigrade foot by means of a bony operation. The triple arthrodesis or stabilisation procedure introduced in the 1920s for gross deformities is still sometimes necessary today for the difficult club foot but is essentially a confession of failure of primary treatment, as it results in a stiff hindfoot.

Outcome

It should be clearly understood by all involved in the surgical management of children with club feet that, even with the very best results possible, the feet will never be completely normal. Some imperfection always persists; a minor residual deformity, loss of movement, shortening of the foot, or thinness of the calf. Based on assessment in relation to mobility, function, and appearance, Green and Lloyd Roberts found a satisfactory outcome in 59% of a series of 70 feet treated in the first six months of life and assessed at an average of 15 years.[1] Comparison with other methods of management in previously reported series is difficult because of their relatively early age of review, or because of less stringent criteria of success. Turco, in a report on 33 feet reviewed 10–15 years after a radical one stage correction performed, between 1–2 years of age, found a satisfactory outcome in 84%.[7] He concentrated, however, on form rather than function and mobility and excluded the ability to play games and the associated aching that sometimes follows.

Overall, it is the preservation of useful movement, particularly that of the ankle, that is the key to success, and minor residual deformity is of little consequence.[8]

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Original articles

Early onset anorexia nervosa

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SUMMARY This paper describes 48 children, aged 14 years or less, who met diagnostic criteria for anorexia nervosa modified from Morgan and Russell.[1] The characteristics of the sample (13 boys and 35 girls) are described along with features of the illness, associated family characteristics, treatment in hospital, and a brief description of treatment. Difficulties in diagnosis are addressed, with reference in particular to the high incidence of depression in this group. Finally, the importance and difficulty of close paediatric/psychiatric liaison in diagnosis and treatment is emphasised.

Among children presenting with wasting conditions, an increasingly recognised proportion have neither malignancy nor other serious physical illness but do have self starvation. This is a report of 48 children, aged 14 years or less, with deliberate self starvation often beginning before the onset of any outward sign of puberty. The published works are replete with reports of various aspects and permutations of eating disorders, but the clinical features and natural history in children remain much less fully explored than in older patients Most reports contain few children, and statements about findings are usually made with reference to older patients. These studies usually address only questions of differences and similarities between a small subpopulation of young patients and a much larger group of older patients with anorexia. The purpose of this study was to supplement our knowledge of one end of the range of anorexia nervosa—that is, childhood.

Review of published reports

There has been increasing recognition recently of the occurrence of earlier onset anorexia nervosa. Although there were occasional reports beforehand,[2] the first major accounts of prepubertal anorexia nervosa occurred in the 1960s.[3–5] Comprehensive reviews have been prepared by Swift[6] and Lask and Bryant-Waugh.[7]

Attempts have been made to isolate differences between earlier and later onset anorexia nervosa. There seems to be a consensus that clinical features of the earlier and later onset groups are essentially similar—namely, denial of emaciation, retention of appetite, power struggles between patients and parents, a high level of depression, and frequent exercising.[4–10] There are characteristics, however, that remain unclear. Irwin, for example, suggested that the course of anorexia nervosa was different in early onset cases, with younger children becoming more emaciated because of less initial body fat and depressive symptoms occurring earlier than in older children.[8] Although well documented in older boys,[11] the incidence and features of anorexia nervosa in younger boys require clarification as few such children have been described.

In the follow up publications there has been controversy about the prognosis of early onset anorexia nervosa, with some authors suggesting that it is associated with a more favourable outcome.[3 4] In a review of this work, focusing particularly on the methodological adequacy of the studies, Swift[6] concluded that the long term results were similar to those found in studies of later age of onset,[12 13] and this has been confirmed by the most recently reported series.[14] Although, for example, normalisation of weight is common, residual clinical disease—for example, poor social relationships[15]—is often apparent at follow up. This underlines the severity of the disorder, and combined with Russell's findings that premenarcheal anorexia nervosa has serious implications for the progress of puberty,[16] points to the importance of clarifying the characteristics of this disorder.

Aim

The aim of this paper was to characterise the antecedents, clinical manifestations, patterns of family organisation, and treatment in hospital of 48 children with determined food avoidance and weight loss beginning before their 15th birthday.

Methodology

A survey of the clinical records of all children seen at our hospital between 1960 and 1984 was carried out to seek cases of anorexia nervosa in children less than 15 years of age. Criteria for inclusion in the study were the criteria for diagnosis of anorexia nervosa modified from Morgan and Russell (Table 1).[1] Clinical records were analysed by personnel with psychiatric and psychologic backgrounds using coded review forms and operationalised definitions of various diagnostic and outcome categories, interventions, etc. Clinical situations or questions not covered by the definitions were resolved at conjoint project meetings. A subgroup of files were reviewed by multiple raters, and the concordance of their findings was 0·93. Recognising that most clinical records are insufficiently detailed, etc, to provide a completely satisfactory data base for research, we have attempted to quantify this deficiency in our sample. Entries in reviewed records yielded the necessary information at the rate of 90%. Accordingly, we believe this sample sufficiently large to justify our attempt to elicit information toward clarifying our understanding of this serious disorder in children. Most data are descriptive. Inferential statistical comparisons were made, however, on some sample characteristics and on one outcome measure.

Results

Demographic findings. Demographic features of the sample of 35 girls and 13 boys are shown in Table 2. Mean age at which symptoms first caused concern was 11·7 years and ranged from 7·75 to 14·33 years, while mean age at referral was 12·34 years, with a range of 8·17 to 14·83 years. Sexual development varied, with 23 being prepubertal (seven boys and 16 girls), 20 pubescent (six boys and 14 girls), and five postpubertal (all girls) Twenty one were the youngest child in their families and 13 the oldest. Six had no siblings and there was one set of twins. Twenty two children were from families of social classes I and II and 21 from classes III and IV as defined by parental occupation according to the Registrar General's classification.[17]

Table 1 *Diagnostic criteria of anorexia nervosa modified from Russell[1] used for inclusion in study*

1 Determined food avoidance
2 Weight loss or failure to gain weight during the period of preadolescent accelerated growth (10–14 years) in the absence of any physical or mental illness
3 Any two or more of the following
  (a) preoccupation with body weight
  (b) preoccupation with energy intake
  (c) distorted body image
  (d) fear of fatness
  (e) self induced vomiting
  (f) extensive exercising
  (g) purging (laxative abuse)

Clinical features. The variation in clinical features is shown in Table 3. Nutritional state was assessed using weight to height ratios derived from the Tanner-Whitehouse standards[18] in which less than 80% represents significant wasting. Of our sample, 40 (83%) were significantly wasted at the time of referral. The clinical features of our cases in decreasing frequency were food refusal, wasting, depression, fear of fatness, distorted body image, self induced vomiting, excessive physical exercise, obsessional behaviour, bingeing, and laxative abuse.

The major expressed reasons for food refusal were fear of fatness, abdominal pain, and feelings of fullness or nausea (Table 4). Only three children cited loss of appetite as the predominant reason for not eating. The clinical features often varied considerably during the course of the illness, leading to the diagnosis often being missed. For example, a child might present with depression or abdominal pain and only later show the more typical features of

Table 2 *Demographic features of the sample*

No of patients	48
Sex (M F) (No (%))	13 35 (27 73)
Age at onset (years) (range (mean))	7 7–13 7 (11 7)
Age at presentation (years) (range (mean))	8 2–13 9 (12 3)
Social class (No (%))	
I	7 (16)
II	15 (35)
III	17 (40)
IV	4 (9)
Stage of puberty (M F Total (%))	
Prepubertal	7 16 23 (48)
Pubescent	6 14 20 (42)
Postpubertal	0 5·5 (10)
Ordinal position (No (%))	
Only	6 (13)
Eldest	13 (27)
Middle of 3+	21 (44)
Youngest	8 (17)

Table 3 *Clinical manifestations of children with anorexia nervosa Values are No (%)*

Food refusal	48 (100)
Wasted	40 (83)
Clinically depressed	27 (56)
Afraid of becoming fat	27 (56)
Distorted body image	24 (50)
Self induced vomiting	19 (40)
Exercising excessively	16 (33)
Obsessions or compulsions	14 (29)
Binge eating pattern	6 (13)
Laxative abuse	4 (8)

Table 4. *Reasons given for food refusal by children with anorexia nervosa. Values are No (%)*

Fear of becoming obese	27 (56)
Feelings of nausea or fullness	6 (13)
Abdominal pain	5 (10)
Loss of appetite	3 (6)
Dysphagia	2 (4)
Weight reduction	2 (4)
Other	5 (10)

Table 5 *Features of the families of children with anorexia nervosa*

	n*	*Present (No (%))*
Overinvolvement	38	31 (82)
Failure to resolve conflict	35	31 (89)
Parental control inconsistent or otherwise inadequate	34	29 (85)
Communication problems	32	24 (75)
Overprotective parents	34	20 (59)
History of anorexia nervosa or other mental illness	48	20 (42)
Anomalous family structure	48	13 (27)

*n Refers to number of families for whom the information was available

anorexia nervosa; alternatively, as the eating difficulties seemed to diminish so other symptoms would come to the fore.[7]

In each case a complete assessment of family organisation and function complemented the psychiatric and paediatric investigations of the child (Table 5). The following distortions of interactions among family members were common and considered important in perpetuating the problem.

> Overinvolvement (lack of privacy for individual family members) was present in 31 of 38 cases.
>
> In 24 of 32 families there were pervasive communication problems such as individuals often speaking for or interrupting others, individuals disqualifying or not listening to the statements of others, or the frequent issuing of mixed messages.
>
> Parenting was considered inadequate or inconsistent in 29 of 34 families and overprotective in 20 of 34 families.
>
> Over half the families possessed multiple adverse characteristics.

A history of anorexia nervosa existed in four first degree relatives of patients, while other forms of mental illness, specifically depression, anxiety, or alcohol abuse occurred in 21 (44%) cases.

Treatment in hospital. Many aspects of management varied during the 24 years of study. Four patients received only outpatient care. Twenty five (52%) were initially admitted to a paediatric ward and 16 (33%) remained on the paediatric unit for their entire admission to hospital. Twenty eight (58%) were admitted or later transferred to a psychiatric unit The duration of admission to hospital ranged from one week to over six months, with 20 (42%) being discharged by three months and 36 (75%) by six months. Artificial feeding was seldom necessary, but two patients received courses of nasogastric feedings and one required intravenous alimentation. The treatment approaches used were individual psychotherapy in 17 (34%) cases, behaviour modification with individualised rewards for weight gain in 31 (65%), and conjoint family treatment in 34 (71%). During the last few years of the study a combined treatment programme included family treatment and admission to hospital in a therapeutic environment providing daily individual counselling sessions and encouragement to eat, with or without a behaviour modification programme.

Findings at end of treatment. Full details of the treatment are published elsewhere.[7] Most patients improved during admission to hospital (four patients never required admission). Thirty (68%) achieved all therapeutic goals, including restoration of normal mood, improved social skills, satisfactory relationships with peers and authority figures, untroubled eating patterns, and weight gain. Thirty five (80%) gained significant weight but fell short in one or more of the psychosocial areas. For the group the mean weight/height was 72·83% at admission and 86·98% at discharge. The 14·15% difference is a significant increment ($p<0·01$). Nine patients failed to gain weight during admission to hospital; one patient gained weight only with parenteral nutrition but died during admission to hospital.

Placements after discharge from hospital varied (Table 6). Forty children were discharged to the care of their parents. Five were transferred to other hospitals, one child went into full time boarding school, and one (admitted from another hospital) went to a foster home One child died from exsanguination after repeated oesophageal tears secondary to pernicious vomiting.

The results of a long term follow up are to be published shortly.

Table 6 *Placements after discharge from hospital in children with anorexia nervosa Values are No (%)*

Parental home	38 (79)
Adoptive home	2 (4)
Foster home	1 (2)
Other hospitals	5 (10)
Full time boarding school	1 (2)
Deceased	1 (2)

Discussion

A number of important points emerge from this study, which we believe to contain the largest reported series of early onset anorexia nervosa. The proportion of boys is significantly higher (27·1 *v* 10·2%, $p<0·05$) than a compilation of comparable series reported by Swift[6] but concordant with a high incidence in two recent series.[14 19] Certainly, however, the proportion is far higher than in adult anorexia nervosa (6·4%) ($p<0·01$).[20] The clinical features, however, are the same in both boys and girls. Youngest children (who formed 44% of the study population) are significantly different ($p<0·001$) from census figures (15%) but similar to two other series (40% and 44%).[5 6] Finally, the sample is biased towards social classes I and II (46% of the study population) compared with the general population (17%) ($p<0·001$).

Perhaps these findings can be most easily integrated into the conceptualisation of anorexia nervosa as a distorted or overly focused struggle for self control and autonomy. Struggles require adversaries and in our opinion the propensity of parents to be positioned to adopt this role varies with the age, sex, and ordinal position of pregnancy. In our culture parents are more likely to be intrusively involved with and/or overly controlling of girls and youngest children than offspring in complementary categories. In some of these families parents will not withdraw in response to the child's emancipatory stirrings. Given this situation, some children will attempt to resolve the ensuing conflict by focusing the controversy on food and control of intake. This is an effective option only if the reduction in food consumption is consistently at their discretion—that is, not subject to availability or threatened by the family's financial resources.

Our findings indicate the importance of anorexia nervosa from the paediatrician's viewpoint. Eighty three per cent starved to the point of wasting, and all children required careful monitoring of their energy intake and electrolyte balance. Many of the children were thought initially to have some other serious medical condition, such as malignancy or Crohn's disease.

Fifty two per cent of our sample spent at least some time on a paediatric ward, although the national figure is likely to be higher given the shortage of psychiatric facilities. Elsewhere we discuss the problems of treating these children.[7] The conflicts within the treatment team are usually between paediatric and psychiatric personnel and also medical and nursing staff. Children with anorexia seem to be particularly adept at creating conflict, not from planned behaviour or malice, but as a habitual way of relating, generalised from intrafamily interaction. The divisiveness is so regularly problematic that routine discussions among team members[21] should be held to identify and resolve the problem.

The presence of depressive symptoms in 56% of our cases is similar to findings in other studies and presents a confounding ingredient to the diagnostician. Certainly, primary depression can present with reduced food intake and weight loss. The other features of the illnesses are usually sufficiently different to allow differentiation in each case (Table 7), but sometimes this can only be accomplished after a period of observation in hospital. Chronic physical conditions may also present diagnostic differences, especially when laboratory confirmation is elusive and a reactive depression is present

Therapeutically, the most important recent advance has been the addition of family treatment to treatment regimens. The type and frequency of distorted patterns of family interactions have been well documented.[22 23] For this reason hospital induced improvement cannot be expected to persist when the children are returned to a family environment of unresolved conflicts, inadequate boundaries between individuals and generations, and communication problems. These family features perpetuate the symptoms and are the reason for the central position of treatment for the entire family. (Russell GFM, Eisler I, Szmuckler G, Dare C. A controlled study comparing family and individual therapy in the treatment of anorexia nervosa. Presented at the Royal College of Psychiatrists, 1985.)

Conclusions

This group of mostly preadolescent children with growth failure and determined food avoidance represents early onset anorexia nervosa. In this series of cases the diagnosis and referral for psychiatric treatment were often delayed, while physical conditions were repeatedly excluded. The

Table 7 *Differentiation of anorexia nervosa from depression according to certain features*

	Anorexia nervosa	*Depression*
Determined food avoidance	Always	Rarely
Appetite	Normal	Decreased
Activity level	Increased/normal	Decreased
Weight loss	Always	Usually
Patients affirm thinness	Sometimes	Always
Wish to gain weight	Rarely	Usually
Vomiting	Common	Rarely
Bingeing	Occasionally	Never

cluster of weight loss and determined food refusal should trigger an exploration for other symptoms of anorexia nervosa—that is, fear of fatness, preoccupation with body weight, or calories, distorted body image, vomiting, laxative abuse, overly intrusive and controlling parent, other types of faulty parenting, and unresolved conflict within the family. The presence of any one of the first five features and one other feature would suggest the expedience of a simultaneous psychiatric and medical evaluation.

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Reactions to dietary tartrazine

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SUMMARY Double blind challenges with tartrazine and benzoic acid were performed in hospital in 24 children whose parents gave a definite history of a purely behavioural immediate adverse reaction to one of these substances. The patients, whose ages ranged from 1·6 to 12·4 years, were on a diet that avoided these items, and in all there was a clear history that any lapse of the diet caused an obvious adverse behavioural reaction within two hours. In no patient was any change in behaviour noted either by the parents or the nursing staff after the administration of placebo or active substances. Twenty two patients returned to a normal diet without problems, but the parents of two children insisted on continuing the diet. While popular belief has it that additives may have harmful behavioural effects, objective verification is required to prevent overdiagnosis.

It is becoming common for parents to report that their child's behaviour problem is caused by an adverse reaction to a food additive and in particular to tartrazine. This study is an attempt to verify these observations.

Patients and methods

Between January 1981 and the end of July 1986, out of roughly 700 children referred to a unit with a special interest in eczema and severe atopic disease, 30 children were seen whose parents provided a definite history of a purely behavioural immediate adverse reaction to a food additive. Those whose parents were merely suspicious about food additives were not studied. Children in whom a behavioural change was only one of several features of an adverse reaction to an additive, such as an acute attack of eczema or asthma, were also not studied. This report concerns the 24 patients whose parents were willing for their observations to be exposed to objective validation. In one patient the parents agreed to double blind challenges but then telephoned to report that their child had suddenly grown out of additive intolerance and food allergy. At the time of study, all the patients were on a diet that avoided the additives and any other foods under suspicion, and in all there was a clear history from the parents that any lapse of the diet caused an obvious adverse behavioural reaction within two hours.

In all patients a record was made of the reasons given by the doctor for the referral and of the specific behaviour problems noted by the parents. The history and observations in the clinic and on the ward were used to see if the child's behaviour problems met the American Psychiatric Association DSM-III criteria for the diagnosis of 314·01, attention deficit disorder with hyperactivity[1] (more commonly simply called hyperactivity in this country). A family and personal history of atopic disease was recorded and details of the diet noted. The parents of all 24 patients reported that tartrazine was the additive that caused the most severe adverse reaction, and in six there was a history of a similar adverse behavioural change to benzoic acid.

With the parents' agreement, the children were challenged double blind with tartrazine and benzoic acid separately. The challenges were performed on a general medical paediatric ward. Twelve children were inpatients and 12 came to the ward as outpatients. The parents of the outpatients knew on which day the challenge was to be performed, but for the inpatients neither the parents nor the nursing staff knew on which days challenges were to be performed, and the child was given the vehicle drink (orange juice or Ribena) throughout admission.

Each child was allowed to play normally on the ward, in both the play room and the corridor, and was allowed to mix freely with inpatients and visitors. Each child was observed by at least one parent and by the nursing staff, each of whom were asked to keep a timed but separate record of any change in the child's behaviour. No specific scoring system was employed. While the parents knew what symptoms to look for, the nursing staff were not given specific details about an individual patient and were just asked to record any change at all in the child's behaviour. Challenges with tartrazine were performed by dissolving 50 mg in a coloured drink to which the child was said to be tolerant, which in 19 cases was pure orange juice from a carton and in five was Ribena, a blackcurrant drink that also contains sodium benzoate and sodium metabisulphite. A second tartrazine challenge using 250 mg was performed at least two hours after the first challenge. After the challenge with tartrazine, but on a separate day, all patients were challenged with benzoic acid, the procedure and dosages being the same as for tartrazine. All drinks were administered by a member of the medical staff, the child used a straw, and neither the parents nor the nursing staff were allowed to see the drink at close quarters. Despite these precautions one 10 year old child accidentally spilled orange juice containing tartrazine and immediately noticed the colour staining his skin.

Results

Nineteen of the 24 patients (79%) were boys, a sex ratio of 3·8. Their ages ranged from 1·6 to 12·4 years, with a mean age of 5·2 years. Formal developmental assessments were not performed, but none of the patients was mentally retarded. One patient was seen in 1981, one in 1982, one in 1983, four in 1984, seven in 1985, and 10 in 1986. Twenty three of the 24 patients were on a diet excluding a mean of 23 food items, ranging from two (colouring agents and preservatives each counted as one food) to 38. The other child was on a diet comprising only three foods. In nine children the only exclusions from the diet were colouring agents and preservatives. The patients had been on a diet for a mean of 24 months, ranging from one to 36 months.

The most common reason for referral given in the referral letter was abnormal behaviour (15 cases), followed by a request for supervision of the diet (six), patient's behaviour only partly responded to dietary measures (five), mother requested referral to allergy clinic (three), initial response to diet followed by relapse (two), parents wanted validation of adverse reaction to additive (two), and parents seeking 'underlying reason' for adverse reaction (one). The behaviour problems reported by the parents are given in the Table Nine of the patients (38%) had a first degree relative with a history of atopy, and 11 patients (46%) had a personal history of atopic disease, which was eczema in six (with rhinitis in one), asthma in four, and urticaria triggered by foods in one. Ten patients (42%) had neither a personal nor a family history of atopy. Six of the patients (25%) fulfilled the DSM-III criteria[1] for attention deficit disorder with hyperactivity.

Table *Behaviour problems reported by the parents*

Poor sleeping	12
Runs about or climbs on objects incessantly	11
Temper tantrums	10
Aggressive behaviour	8
Unable to sit still	7
Poor concentration	4
Violent outbursts when under stress	4
Uncontrollable	4
Pulls things off shelves in supermarket	3
Accidents/injuries resulting from jumping or rushing	3
Persistent crying as a baby	3
Disobedient or defiant	3
Incessant drinking	2
Often bursts into tears	2
Unable to play constructively	2
Lives in a world of his own	1
Easily led	1
Hysterical if exposed to water	1
Unhappiness	1

Of the 24 patients, 18 were described by the nursing staff and the parents as behaving quite normally throughout the time of observation, with no detectable change in behaviour with or after placebo or active challenges. There were four children who attended as outpatients, whose parents realised at the end of the first day that there had been no reaction to placebo or active preparation (tartrazine). These four parents suggested that there was no point returning for the second set of challenges and these four children were not challenged with benzoic acid. The other six children, all of whom were studied in inpatients, were regarded by the nursing staff, on clinical grounds, as having behaviour that was in some way abnormal, such as frequent tantrums, aggressive behaviour, or pronounced overactivity. In one of these children, who was admitted to hospital with her mother, the child's temper tantrums (the main complaint) were so gross, prolonged, and frequent that it was initially unclear whether she could be contained on the ward. Her double blind challenges were delayed for four days to see if any spontaneous improvements might occur, but there was no improvement and the challenges were performed without any alteration in the frequency or duration of tantrums with either placebo or active preparations. In the other five the behavioural abnormalities, as observed by the nursing staff and the parents, were unrelated in time to the administration of either placebo or active challenges. In one of these five patients testing was delayed for two days because the child absconded from the ward. In short, in no patient was any change in behaviour noted either by the parents or the nursing staff after the administration of placebo or active substances.

The results of the double blind challenges were analysed in the presence of the parents. Having found a lack of adverse reaction to tartrazine and benzoic acid, the parents were advised to place their child on an entirely normal diet. This was performed in hospital for all 12 inpatients and on the ward for outpatients where the parents were nervous to proceed. Of the 24 patients, 21 returned to a normal diet and remained on it without any food related problems at follow up. The parents of one patient, who was only on three foods at the time of admission, was unable to accept that the child was not food intolerant, and when new items of food were added to the diet they insisted that as a result the child had loose stools, skin rashes, and an adverse behavioural change, although none of these events were detectable to the nursing or medical staff. This child remained on a very restricted diet against our wishes. The parents of a second child were pleased that their daughter was able to eat normal food without adverse effect but continued to insist that she should avoid colouring agents not only in the diet but also in such items as paints. They alleged that on days when the child had been allowed to use paint at school tantrums and aggression were noted in the evening, and at one stage they threatened to withdraw her from school when the teachers would not agree to the child being excluded from painting. After further counselling they agreed to allow the child normal exposure to all forms of colouring agent. The parents of a third child declined to permit resumption of a normal diet and defaulted from follow up Follow up information was available in all the other patients.

After resumption of a normal diet the parents were given simple advice about the practical management of the behaviour problems that had been described. Referral to the child psychiatry department was offered to the parents of 16 patients where it was anticipated that the parents might benefit from further counselling. Thirteen accepted this offer, but four later wrote to the psychiatrist and reported that the child's behaviour had improved and that attendance was therefore not needed.

Discussion

A drawback to this study is that it was performed in hospital. It is well known that children often behave differently in new or unfamiliar situations, and the DSM-III criteria for attention deficit with hyperactivity clearly recognise this: 'Because the symptoms are typically variable, they may not be observed directly by the clinician. . . . Signs of the disorder may be absent when the child is in a new or a one-to-one situation'.[1] Thus the failure of the challenges to elicit a change in behaviour may be attributable to unfamiliarity of the ward environment. Furthermore, it is the belief of certain clinical ecologists that 'allergies' are cumulative, implying that a trigger such as an additive might only operate when the child is also exposed to other antigens such as house dust mites Against these objections are the patients whose behaviour difficulties continued unabated, the fact that the parents reported that tartrazine had consistently produced adverse reactions under any circumstances, and the absence of adverse reactions on resumption of a normal diet at home. A further objection to the present study is that objective measures of changes in behaviour were not used and that the study relied on the crude and unstructured observations of the parents and non-psychiatrically trained nursing staff As all the parents had previously reported dramatic and obvious behavioural changes after the administration of tartrazine it seemed reasonable to expect that the parents and nursing staff should be able to recognise such changes had they occurred.

This study was undertaken in hospital because it is almost impossible to disguise tartrazine, which in high concentrations gives a characteristic appearance to food and drink that is quite obvious to an adult who administers it. All drinks were taken through a straw because of the characteristic staining of the skin around the mouth after drinking solutions containing tartrazine. Capsules were not used because of the obvious bright colour of those containing tartrazine. For these reasons, investigations using high doses of tartrazine and performed at home[2] are likely to be unsatisfactory because the presence of tartrazine is quite evident, even in highly coloured food or drink.

In short, this study of 24 children showed that parents' reports of adverse behavioural changes after ingestion of tartrazine or benzoic acid could not be validated objectively when exposed to the test of double blind challenges. This is consistent with similar previous studies.[3–7] This study does not exclude the possibility that there are rare children who have purely behavioural effects as a result of ingestion of additives such as tartrazine or benzoic acid It does show, however, that parents' beliefs in the behavioural effects of tartrazine or benzoic acid are often groundless and are unreliable. This is in contrast to the situation in children with atopic disease, such as asthma or eczema, where tartrazine and benzoic acid may act as triggers,[8 9] and where better control of the disease is often accompanied by a pronounced improvement in behaviour and concentration. Thus in one study of 76 patients where diet was said to contribute to behaviour disorders a large proportion of the children had atopic disease.[2]

An important feature of this study is that it shows how paediatricians can manage the increasing clinical problem of parents' anxieties about diet without being dismissive or confrontational. Although only two challenges were given, this was convincing to the parents, it allowed them to permit the reintroduction of a normal diet, and it helped them to view their child's behaviour differently and accept management help. Challenges with other food substances may also be required if parents are convinced that these are affecting the child. We need to learn how to help children whose parents insist on keeping them on very restricted diets; there were two such patients in the present series. Our own major effort has been to try and prevent nutritional deficiencies,[10] but this does little to avoid the social isolation and possible emotional harm that results from inappropriate, long term, and extreme dietary measures. It is possible to view such cases as being part of the range of child abuse,[11] but this is probably a last resort.

Why do parents attribute behaviour disorders to additives? Many of the parents in this study said that they first learnt of the possible importance of additives through the media, in contrast to the situation in, for example, urticarial allergic reactions to egg, where the parents' observations are the first event. Suggestion as the result of reports in the media is probably combined with an increasing general interest in the nutritional content of food. Most of the children in this study had been labelled hyperactive, although only six met the DSM-III criteria for this disorder. It is understandably attractive for parents of children with behaviour problems to have available a diagnostic label and an exogenous cause. Parents are usually but not always right about a child, and they cannot be objective. While popular belief has it that additives may have harmful behavioural effects, objective verification is required to prevent overdiagnosis.

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Remission induced by an elemental diet in small bowel Crohn's disease

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SUMMARY Seventeen children with active Crohn's disease of the small intestine were entered into a randomised control trial comparing the efficacy of an elemental diet with that of a high dose steroid regimen. Eight children received an elemental diet (Flexical) through a nasogastric tube for six weeks, followed by reintroduction of food over six weeks during which the Flexical was stopped. Seven children were given intramuscular adrenocorticotrophic hormone followed by oral prednisolone with sulphasalazine. Two children were withdrawn from the trial. The elemental diet was equally effective in inducing an improvement in Lloyd-Still disease activity index, erythrocyte sedimentation rate, C reactive protein and albumin concentrations, and body weight as the high dose steroid regimen. Linear growth, assessed from height velocity over six months, was significantly greater in the children receiving an elemental diet.

Treatment with high dose steroids is the conventional treatment for inducing a remission in Crohn's disease both in adults[1] and in children.[2] Enteral nutrition with elemental diets where nutrients are supplied free of intact protein (nitrogen being supplied by amino acids and oligopeptides) has also been used for both adults[3 4] and children.[5 6] Such specific nutritional treatment has usually been reserved for the complex case and is often used as an adjunct to treatment with steroids.

Table 1 *Age, sex, pubertal state, and sites of bowel inflammation of the cases on entry into the trial*

Case No	*Age*	*Bone age*	*Sex*	*Stage of puberty (and after six months)†*	*Site of inflammation*
Group treated with steroids					
1	13 0	9 1	M	2(2)	Ileum
2	12 7	12 3	M	1(3)	Ileum caecum
3	14 4	14 7	M	5	Ileum
4	16 3		F	5	Ileum, caecum
5	14 4	11 6	M	2(3)	Ileum
6	11 9	13 2	M	3(5)	Ileum, transverse colon
7	10 3	9 2	M	1(1)	Ileum, caecum
8	8 6	8 4	F	1(1)	Ileum
Group fed elemental diet					
1	12 7	9 3	F	1(1)	Ileum
2	13 3	11 2	M	2(4)	Jejunum, ileum, caecum
3	11 2	10 6	M	1(1)	Jejunum, ileum
4	12 8	13 4	M	1(2)	Ileum
5	11 4	13 3	F	1(2)	Ileum
6	17 2		M	5	Ileum, rectum
7	12 7	9 7	F	1(1)	Ileum, colon
8	14 5	14 5	M	2(3)	Ileum
9	16 0	15 3	M	5	Ileum

*Withdrawn from the trial
†Stage of puberty is expressed as genitalia stage in boys and breast stage in girls

Growth retardation has been recognised as an important clinical feature from the time of the first descriptions of Crohn's disease in children.[7 8] It is also a well recognised complication of treatment with steroids in children.[9] In the doses required to induce a remission in children with Crohn's disease, steroids also often produce Cushingoid features. The use of elemental diets is not associated per se with such complications and healthy volunteers have been maintained on them for long periods.[10]

As there has been no study comparing the relative effects of an elemental diet and steroids to induce a remission in Crohn's disease of the small intestine in children a study was undertaken to compare these two therapeutic regimens in relation to their ability to induce a remission by standard criteria. The opportunity was also taken to compare the effect of linear growth of these two modes of treatment.

Patients

Seventeen children, 12 boys and five girls, aged from 8·6 to 17·2 years, were studied at our hospital (Table 1). Seven of the children were prepubertal and 10 pubertal. Patients attending the paediatric

inflammatory bowel disease clinic were entered into the trial if they satisfied the following criteria:
(i) Crohn's disease of the small bowel shown by barium follow through and confirmed by ileal histology of endoscopic biopsy specimens.
(ii) Clinical relapse of sufficient severity to warrant treatment with high dose steroids.
(iii) No treatment with steroids for the previous 12 months.
(iv) Incomplete skeletal maturation.
(v) Domiciled in England (to facilitate follow up).

Methods

Auxological assessment. All the patients underwent measurements of stature by a trained clinical auxologist according to the method of Cameron[11] Pubertal development was assessed using the criteria of Tanner.[12] Bone age was assessed by the same observer using the TW2-RUS method[12]

Treatment regimens. The subjects (Table 1) were randomly allocated to receive either treatment with drugs (high dose steroids and sulphasalazine) or dietetic treatment as an elemental diet. (Both forms of treatment were explained to both parents and children. Informed consent was obtained and any child withdrawn from the trial was to be given treatment with drugs.)

All children were admitted to hospital for one week. The first group received high dose steroids given as adrenocorticotrophic hormone (2 IU/kg/day) intramuscularly for five days followed by oral prednisolone (2 mg/kg/day to a maximum of 30 mg/day). They were also started on sulphasalazine (50 mg/kg/day).[2] No specific dietetic advice was given as this is the usual practice in such children

The second group was treated with an elemental diet, Flexical (Table 2) by nasogastric tube. They were otherwise given nothing by mouth. The daily energy requirement of a particular child was determined using the recommended daily allowance[13] based on his age and weight. As the energy content of Flexical is 4·2 kJ/ml the total daily volume of feed could be calculated. The rate of infusion was adjusted so that a child could take the feed in the evening and overnight and so attend school In the ward the concentration of the diet was built up to full strength over four days Patients were taught how to pass a fine bore nasogastric tube, which was changed at home at least once a week. (Sulphasalazine was continued in two children who were receiving this drug at the start of the study but otherwise was not given to this group.)

After one week in hospital the children were managed as outpatients. The dose of steroids was gradually reduced after three weeks in the steroid group, aiming for an alternate day regimen of 10 mg by 12 weeks Foods were individually introduced after six weeks in those receiving elemental diet, a new food being introduced every four days (Table 3). The energy content of the new foods taken was monitored every two weeks by a dietitian, who reduced the elemental diet accordingly. The Flexical was always stopped by six weeks after the start of the food reintroduction.

Table 2 *Composition of Flexical (per litre of full strength formula)*

Energy (1003 kcal [4212 kJ])
Osmolality (550 mOsm/kg)

Protein (22 5 g)
  Enzymatically hydrolysed casein supplemented with l-tyrosine, l-tryptophan, and l-methionine

Carbohydrate (152 g)
  Glucose syrup solids (140 g)
  Modified tapioca starch (12 g)

Fat (34 g)
  Soy oil
  Medium chain triglycerides

Minerals
  Calcium (600 mg (15 mmol))
  Chloride (1000 mg (28 2 mmol))
  Magnesium (200 mg (8 2 mmol))
  Phosphorus (500 mg (16 1 mmol))
  Potassium (1250 mg (32 mmol))
  Sodium (350 mg (15 2 mmol))

Trace elements
  Copper (1 mg (15 7 µmol))
  Iodine (75 µg (0 6 µmol))
  Iron (9 1 mg (163 µmol))
  Manganese (2 5 mg (45 µmol))
  Zinc (10 mg (153 µmol))

Vitamins

Table 3 *Food reintroduction programme six weeks after starting Flexical*

Each new food is reintroduced into the diet four days after the previous food in the following order

Potatoes
Lamb
Pears
Chicken
Yeast (Breweres Yeast Tablets)
Wheat (spaghetti)
Bread (wholemeal)
Cabbage
Rice
Apple
Carrot
Beef
Milk
Butter
Cheese
Eggs

A free diet is allowed once these foods have been started

Assessment. Disease activity was assessed using the Lloyd-Still disease activity index score[14] composed of the clinical history, physical examination, packed cell volume, white blood cell count, serum albumin concentration, erythrocyte sedimentation rate (ESR), and appearances on barium meal and follow through examination. Serum C reactive protein concentration was also measured Colonoscopy and ileoscopy were performed with barium examination only at entry into the study. Disease activity was assessed at 0, 6, and 12 weeks and the change at 6 and 12 weeks calculated.

Linear growth was assessed from the heights of the children at entry into the study and six months later. The results are expressed as height velocity standard deviation score for chronological age [15]

Statistics. Comparison between groups at entry into the trial and the changes from baseline values with treatment were assessed using the Student's *t* test for Lloyd-Still disease activity index, ESR, albumin and C reactive protein concentrations, and body weight. Linear growth was compared in the two groups by the Mann-Whitney test.

Results

Two children were withdrawn from the trial. One child (case 4 in the group treated with steroids) developed clinical features of intestinal obstruction and underwent bowel restriction two weeks after beginning treatment with steroids. One child (case 6 in the group fed the elemental diet) was unwilling to forego a normal diet. He was treated with high dose steroids.

There were no significant differences in the two groups on entry into the trial with regard to sex distribution, age, disease activity, height standard deviation score, ESR, and C reactive protein or albumin concentrations (Table 4). Pubertal state was also similar in the two groups.

Table 4 *Clinical features at entry into the trial of the two groups of children who completed the study. Values are mean (SEM)*

	Group	
	High dose steroids	*Elemental diet*
Sex (M/F)	6/1	5/3
Age (years)	12 2	13 1
Lloyd-Still disease activity (%)	61(3)	56(4)
Height standard deviation score	−1 0 (1 0)	−1 1 (1 9)
Erythrocyte sedimentation rate (mm in the first hour)	32(6)	37(3)
C reactive protein (mg/l)	40(11)	43(10)
Albumin (g/l)	37(4)	32(2)

The mean and standard error of the changes in disease activity, ESR, C reactive protein and serum albumin concentrations, and weight were calculated for each treatment regimen (Table 5). The disease activity of the children improved significantly ($p<0\cdot01$) by six weeks with both elemental diet and high dose steroids. The improvement in disease activity index, ESR, C reactive protein and albumin concentrations, or weight of those on elemental diet was of similar magnitude to those on high dose steroids (Table 5). In both groups the ESR and the C reactive protein concentration had fallen into the normal range by six weeks, and the children were therefore biochemically in remission. Moreover, at 12 weeks, when the elemental diet group had already finished the Flexical regimen but the steroid group was still taking a mean of 10 mg/day prednisolone, this improvement was maintained (Table 5)

Mean height velocity for chronological age (Figure) was significantly greater ($p<0\cdot05$) in the elemental diet group than in the steroid group, despite similar gain in weight. Six children in the elemental diet group had a positive height velocity standard deviation score, indicating supranormal growth, compared with only one in the steroid group.

It is not possible to say whether the height velocity data are part of a normal distribution as there are different factors affecting the growth at one time, such as disease activity, pubertal state, steroid dosage, and energy intake. The data were therefore compared using the Mann-Whitney test.

Discussion

This paper shows for the first time that in children an elemental diet is as effective as high dose steroids in treating Crohn's disease of the small bowel No

Table 5 *Changes in Lloyd-Still disease activity index score, erythrocyte sedimentation rate (ESR), C reactive protein, albumin, and weight over six and 12 weeks after the start of treatment Values are mean (SE)*

	Weeks from start of treatment	*Group*	
		High dose steroids	*Elemental diet*
Score	6	17(3)	22(2)
	12	19(4)	22(3)
Erythrocyte sedimentation rate (mm in the first hour)	6	−22(5)	−23(3)
	12	−20(6)	−20(7)
C reactive protein (mg/l)	6	−30(8)	−37(10)
	12	−30(8)	−32(9)
Albumin (g/l)	6	4(2)	1 0(4)
	12	13(4)	10(4)
Weight (kg)	6	4 7(1 7)	3 0(0 7)
	12	7 6(2 5)	5 5(0 9)

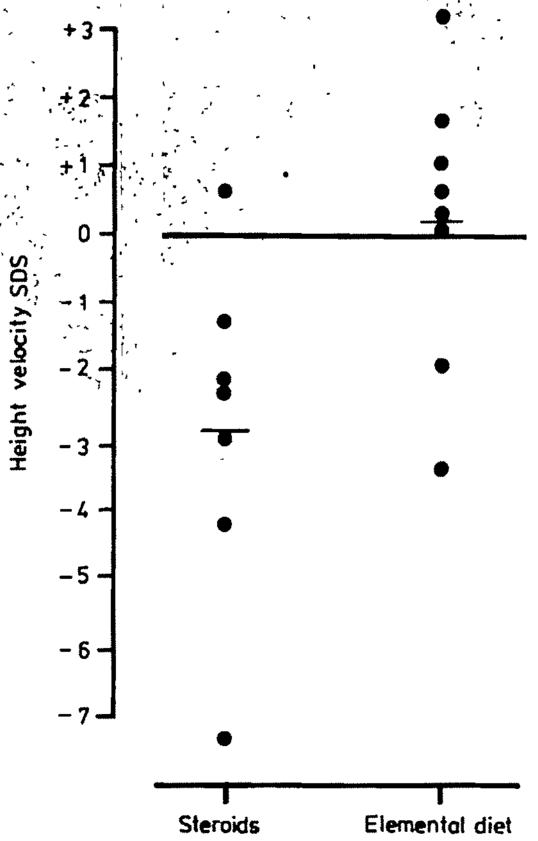

Figure *Height velocity standard deviation score (SDS) for chronological age in the children in the high dose steroid group (mean −2·8) and in the elemental diet group (mean +0·3).*

previous study in children has used a control group for comparison.[6 16 17] The only control trial of elemental diet to date was performed in patients in whom the disease presented long after adult height had been achieved.[3] Moreover, this is also the first study in which the diagnosis has been confirmed in all cases on strict histological criteria.[18] A further feature of the present study is that the duration of hospital stay was the same in both groups, which eliminates bias caused by the possible beneficial effects of bed rest on the activity of Crohn's disease.

Flexical, used in this study because of its adequate zinc content and appropriately low sodium content, is a complete feed in which nitrogen is supplied in the form of amino acids and oligopeptides. The term elemental was adopted to describe the Mead Johnson 3200 AS formula, the prototype for Flexical. Some workers in Europe have used a new term, semi-elemental, to describe diets that contain oligopeptides as well as amino acids; this usage has not been adopted, however, in North America or the United Kingdom. Like other elemental diets Flexical is free of dietary antigens, which may explain its beneficial effect. A change in diet could produce subtle changes, though, in the microflora of the small intestine.

It has been suggested that the immunological reactions that may propagate the inflammation in Crohn's disease are altered by increased energy intake.[16] This is another explanation both for the action of an elemental diet and for high dose steroids as the latter can increase appetite. Measuring energy intake in children who eat at school as well as at home is unreliable and was not attempted in the present study. In addition, as routine dietary advice is not part of current drug treatment any attempt to quantify energy intake accurately would be likely to distort the simple effect of drugs alone.

The unpalatability of the elemental diet was avoided by administering it through a nasogastric tube. All children were taught to pass their own tubes so that those who wished to remove them to avoid embarrassment during school hours could do so. No child was given the opportunity of drinking the diet as an alternative, as previous experience with this method had led to poor compliance. Being unable to eat normal food for six weeks was unacceptable to one child, however, who was therefore not studied.

Linear growth was greater in the subjects treated by elemental diet, but the variety of factors that affect growth make it impossible to say whether or not this was due to active suppression of growth by the steroid regimen.[9] Expression of height velocity in standard deviation scores for chronological age is valid as there is poor correlation of bone age with height velocity in the adolescent growth spurt. There was also no significant difference in the mean delay in bone age between the two groups (Table 1).

In conclusion, treatment by elemental diet is equally effective in inducing remission in Crohn's disease of the small bowel as high dose steroids in children. Moreover, linear growth was significantly greater in those taking an elemental diet, indicating that there is a short term benefit for growth. The long term results of this treatment still need to be evaluated. A recent study of height attainment in children with steroid responsive nephrotic syndrome showed that, while large doses of steroids suppressed growth at the time of administration, there was little effect on ultimate height.[19] This favourable result has not been reproduced, however, in children with Crohn's disease on current treatment. A long term follow up study of 66 children under 16 with small bowel disease who had been treated with steroids revealed that 20 were at or below the third centile two to 14 years later.[20]

We believe that an elemental diet is the initial treatment of choice in children with Crohn's disease of the small intestine, and since completing this study we have used it as standard treatment at our hospital.

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Videourodynamic assessment of diurnal urinary incontinence

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SUMMARY Persistent daytime incontinence is a fairly uncommon but important problem. Videourodynamic studies were carried out in 215 children presenting with this problem in whom there were no neurological signs and who had not responded to simple measures. Over 90% of symptomatic children were shown to have an abnormality, of which over half had detrusor instability and a fifth had the wide bladder neck anomaly. We consider that it is important that these children are fully assessed as many can be helped.

Children with diurnal wetting may be referred to a general paediatrician, paediatric neurologist, paediatric nephrologist, urologist, or psychiatrist. Most of these children have never been reliably dry by day, although occasionally the symptom is of recent onset. They are usually treated empirically.

The advent of the videourodynamic study has allowed us to assess bladder and urethral function more accurately. This investigation has proved invaluable in the assessment and management of the child with a neuropathic bladder and has enabled us to identify those children at high risk of renal damage.[1]

The study consists of a filling and voiding cystometrogram combined with a micturating cystourethrogram.[2] They are recorded simultaneously onto video tape and are viewed side by side using a split screen display so that events occurring in the bladder and urethra can be correlated with pressure changes. As far as the child is concerned measurement of rectal pressure is the only additional feature when compared with a micturating cystourethrogram. A great deal more information, however, is obtained.

Patients and methods

We have reviewed the urodynamic findings in 215 children (with an age range of 3·5 to 16 years) studied at this hospital over the last six years The children were selected for study because of persistent diurnal wetting that had not responded to simple measures such as star charts and timed voiding. Most wet their pants at school on most days and some had to take changes of clothing to school daily. Children with an ectopic ureter were excluded.

All were physically normal and none had neurological signs. Children with nocturnal enuresis alone were not included; indeed, we rarely study these children as it has been found that most have normal bladder function.[3] A careful history is important, however, as it may reveal daytime problems that have not been volunteered by the parent or child.

The studies were all performed using standard urodynamic techniques and urethral catheters. The children were not sedated and failure to carry out a study because of lack of cooperation occurred in less than 5%.

Measurement of urinary flow rate was included as a standard part of the study and provided useful additional information where there was evidence of obstruction to urinary flow—for example, distal urethral stenosis—particularly if high detrusor pressures were being generated in an effort to try and overcome this. If there was a low urinary volume, however, then the flow rate would be reduced. The flow rate could also be measured independently and could thus be checked if it was thought that inhibition had affected this during the study itself.

Results

As can be seen in Table 1 over 90% of the children were found to have an abnormality and in over half this was due to detrusor instability. A fifth of the children had the wide bladder neck anomaly. Some had more than one abnormality, the commonest

Table 1 *Videourodynamic abnormalities found in 215 children with diurnal enuresis*

Detrusor instability	123 (57%)
Wide bladder neck anomaly	45 (21%)
Normal	19 (9%)
Others	
Hypersensitive bladder	10
Large capacity bladder	6
Bladder neck obstruction	9
Urethral stricture	3

Table 2 *Detrusor instability in the group studied*

	No with instability	*Other abnormalities in these children*
Boys	60	8 with occult neuropathic bladder 5 with bladder neck obstruction 3 with past history of urethral valves 2 with wide bladder neck anomaly
Girls	63	7 with wide bladder neck anomaly 3 with occult neuropathic bladder 2 with distal urethral stenosis 1 with vesicovaginal fistula

combination being detrusor instability with wide bladder neck anomaly.

As can be seen in Table 2 there were an equal number of boys and girls with detrusor instability, with ages ranging from 3·5 to 16 years and a mean of 8·9 years in girls and 8·7 years in boys

Forty five children had the wide bladder neck anomaly. Of these, 35 were girls, with ages ranging from 7 to 16 years (mean 10·3 years), seven of whom also had detrusor instability. There were 10 boys with this abnormality, with ages ranging from 8 to 13 years (mean 9·8 years), three of whom had detrusor instability.

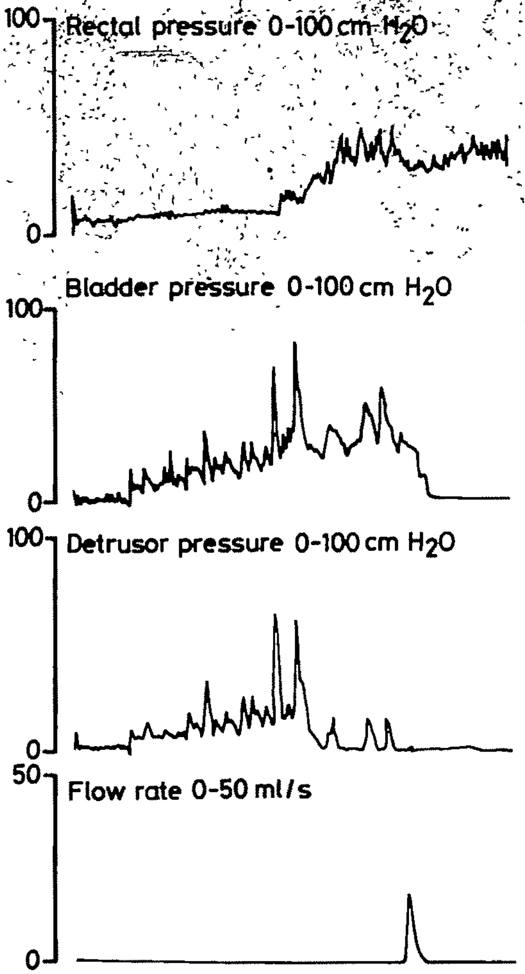

Fig 1 *Cystometrogram, showing unstable detrusor contractions during bladder filling.*

Discussion

Detrusor instability is equally common in boys and girls and is associated with the same type of urge symptoms as in adults The symptoms tend to improve at puberty and there may be a cause and effect relation with vesicoureteric reflux.[6] This abnormality was found in 20% of the children studied who had detrusor instability. Webster *et al* found reflux in 10 of 28 children with detrusor instability.[4] Urine infections have been reported to occur in up to 60%,[4–6] and we found this association in almost 50% of children with detrusor instability None of the chidren, however, had an infection at the time of study.

Urodynamically, the occurrence of unstable contractions is almost always spontaneous, and Figure 1 shows the typical trace obtained in an 8 year old girl who presented with urgency, frequency, and diurnal enuresis. Unstable contractions can be seen shortly after filling begins. These children usually have reduced bladder capacity (capacity=(age in years×25) +25 ml).[1] Characteristically, the detrusor pressure during filling showed a much more pronounced degree of fluctuation than would be expected in adults with instability. Our finding of this abnormality in just over half of our group agrees with the findings of Webster *et al,* who found unstable bladders in 47% of 60 children studied who were neurologically normal but who had micturition dysfunction.[4]

Because the pathophysiology of this condition and the transition from incontinent infancy to continent childhood are poorly understood, we have hesitated in making this diagnosis in children under the age of about 5 years. None the less in 'normal' children in this very young age group (with only minor degrees of reflux) it is usual to find a bladder capacity approximating to the formula given above and a fairly 'stable' detrusor pressure until capacity at which time a single 'normal' detrusor contraction produces voiding, albeit 'involuntary' (unpublished observation). The presence of pronounced fluctuations in the detrusor pressure that do not lead to voiding and a reduced bladder capacity are therefore unusual and we think that they represent detrusor instability in this age group

It is interesting that in younger children instability is almost always spontaneous and the detrusor pressure tends to show low amplitude fluctuations, whereas in older children postural instability is sometimes present and low amplitude fluctuations are less common, as this contrasts with adult practice in which postural or cough induced instability is so much more common, spontaneous instability is less common, and a constantly fluctuating detrusor instability is rare (in the absence of neuropathy). This suggests that the pattern of detrusor behaviour tends to change with time even if the symptomatology does not.

Thirty nine children with detrusor instability had a second study during follow up and 24 had a third. These studies were spaced one to two years apart. During this period the detrusor pressure trace in those that remained unstable tended to become more like that seen in adults with detrusor instability, with discrete phasic waves of pressure interspersed with periods of quiescence.

Incomplete bladder emptying was extremely rare in children with detrusor instability and is therefore unlikely to be related to the increased incidence of urinary infections in this group. It has been suggested, however, that during uninhibited contractions the child voluntarily contracts the external sphincter in an attempt to maintain continence, which increases intravesical pressure, causing mucosal ischaemia, and that this may be a major factor in the development of recurrent infections.[4]

'Milk back' of potentially infected urine may also predispose to infections. Despite the high incidence of infections in this group, impairment of renal function and upper tract problems were rarely seen and had usually been diagnosed when investigating a urinary tract infection, before referral for a videourodynamic study Children with recurrent urinary infections were treated with prophylactic antibiotics.

Anticholinergic drugs now have an established place in the treatment of detrusor hyperreflexia in association with a neuropathic bladder and have also been used in the treatment of instability in neurologically normal children They act by decreasing instability and thereby indirectly increasing bladder capacity. We have found these drugs to be useful in the treatment of children with detrusor instability. We have used either propantheline or oxybutynin. Although these results are encouraging, long term follow up is required, and these results will be reported fully at a later date.

In 1973 Stanton and Williams found the wide bladder neck anomaly alone in 21 of 100 children with persistent diurnal incontinence.[7] They stated that the condition can be recognised by one or more of the following signs: widening of the bladder neck on micturating cystogram; incomplete milk back on micturating cystogram; an open bladder neck on cystoscopy; a low urethral pressure profile; a normal cystometrogram; absence of neurological signs; and absence of distal urethral stenosis. In our experience the condition is associated with a mixture of stress and urge type symptoms, but the presence of stress type symptoms has a strong correlation with the condition in both sexes. It is commoner in girls and tends to improve in puberty in both sexes. It may predispose to genuine stress incontinence in adult life. The abnormality was found more commonly in girls. The diagnosis was made when the bladder neck was seen to be open, throughout the filling phase, at a time when the detrusor was not contracting (Fig. 2). These children may be dry at night

Our findings of 19% with this abnormality compares well with 21% in Stanton and Williams' group. We are currently evaluating the effect of the α adrenergic agonist drug, ephedrine, on this group of children.

Fifteen of the girls had a second videourodynamic study during the follow up and four had a third. None of these girls showed any improvement in

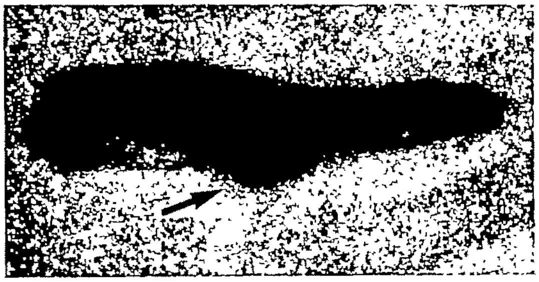

Fig 2 *Photograph taken from videourodynamic study, showing a wide bladder neck (indicated), which was present from the beginning of filling of the bladder*

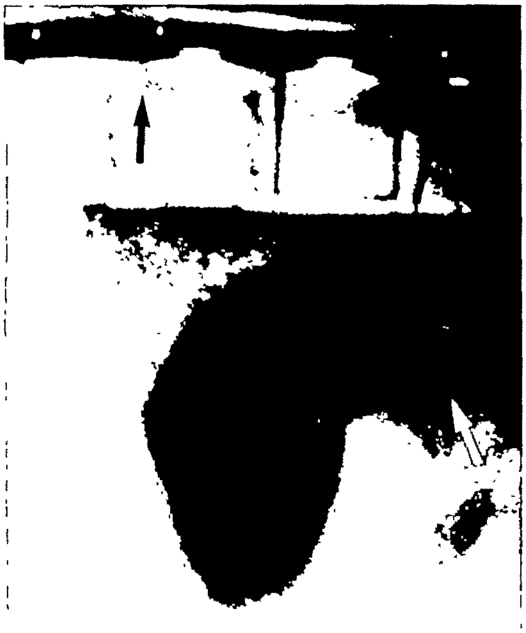

Fig. 3 *Photograph taken from a videourodynamic study, showing voluntary contraction of the distal sphincter (white arrow) to prevent urinary leakage during an unstable detrusor contraction (black arrow)*

bladder neck competence, even though the symptoms tended to improve at the onset of puberty. Equally, we have yet to see a child who has previously been shown to have a competent bladder neck develop this anomaly.

In our group of 45 children (35 girls and 10 boys) seven girls and three boys also had detrusor instability.

The so called 'occult' or 'non-neurogenic' neuropathic bladder was first described by Hinmann and Baumann in 1973[8] and subsequently by other workers[9] [10] and consists of urinary incontinence with some combination of encopresis, heavily trabeculated bladder, urinary infection, vesicoureteric reflux, and a negative neurological examination. All of the investigators noted discoordinate activity between the bladder and external sphincter during detrusor activity. We have certainly seen voluntary detrusor sphincter dyssynergia in children with this problem and this seemed to be a voluntary effort by the child to prevent urine leakage when an unstable contraction occurred (Fig. 3). It may be that the occult neuropathic bladder is an extreme form of an otherwise normal response to unstable detrusor activity.

Soiling in our study group was extremely rare even in the children with an occult neuropathic bladder. One girl with detrusor instability who initially responded well to treatment with drugs subsequently relapsed and started to soil. She was found to have emotional problems related to teasing and underachievement at school and was referred for psychological help.

The third largest group of children in our study (although comprising only 8%) were those in whom no abnormality was found. We have found that many of these children simply cannot be bothered to go and void when their bladders are full. For this reason they can be called 'avoiders'. They tend to have social, educational, or emotional problems and most can be diagnosed clinically Psychological problems may coexist with abnormal videourodynamic findings, and the present study was not designed to look at this relation nor is it concluded that treatment with drugs alone is all that is required. A primarily psychological style of management may well be incomplete, however, in terms of both information and possible treatment.

An important finding in our study was that only 8% of the children had normal studies, and this emphasises the importance of investigating these children. This is best performed by carrying out a combined videourodynamic study. These children cannot be accurately diagnosed on the basis of symptomatology alone. Some have more than one abnormality and this may be missed if a combined study is not undertaken. Finally, we think that many of these children can be helped if accurately assessed, although long term follow up is necessary.

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Successful management of daytime enuresis using alarm procedures: a randomly controlled trial

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SUMMARY Forty four children with daytime wetting were included in a randomly controlled trial of two alarm devices, a contingent one that sounded when wetting occurred and a non-contingent one that went off from time to time unrelated to wetting events. A quota allocation system ensured comparability between treatment groups. Two thirds responded to an alarm by becoming dry. The non-contingent alarm produced as good a response as the contingent one and is recommended for routine use in children with diurnal enuresis. Twenty three per cent of those who responded to treatment relapsed up to two years after completion of the trial.

Various methods of management have been found to be effective in the treatment of nocturnal enuresis, particularly the use of the pad and bell alarm device. Unfortunately, there has not yet been comparable success in dealing with diurnal enuresis.[1–3] The enuresis alarm for bed wetting provides a loud auditory stimulus immediately after the occurrence of the wetting event. It is possible to produce a similar effect for daytime wetting using a pants alarm.

This study was set up to evaluate a contingent alarm system for the treatment of diurnal enuresis using a randomly controlled trial. Children who did not receive the device being tested were managed with what seemed to be an identical alarm but which in fact merely emitted a similar loud tone about every two hours, whether wetting had occurred or not.

Patients and methods

Children aged 5 to 15 attending a children's enuresis clinic were selected for inclusion in the trial. Daytime wetting had to be sufficiently common and severe to make it the main problem complained about by the mother. For most of the children the pants became so wet each day that urine soaked through to trousers or skirt; it was rare, however, for there to be a puddle on the chair seat or floor. About two thirds of the children were referred by consultant colleagues (tertiary referral) and the other third by general practitioners or clinical medical officers. Any children identified as having severe urinary tract abnormality were excluded; urinary tract infections were treated before the child was included in the study. Children with very severe social or psychological problems that made them unsuitable for routine management in a paediatric outpatient clinic were also excluded. Nevertheless, the sample of cases included in the study was virtually a consecutive series of children presenting with troublesome daytime wetting; only two were excluded because of being too disturbed for paediatric management.

Fifty cases were collected, but in one instance the family refused to participate, in another the child developed diabetes mellitus, and for four others treatment was not thought to be necessary as there was a period of at least seven days without wetting during the baseline period. Therefore, 44 children were included in the trial and allocated to one of the two treatment groups.

The mean (SD) age of those included was 8·5 (2·1) years (range 5·0 to 13·0 years), and 35 were girls. Social class on the Registrar General's classification was 15 in classes I or II, 22 in class III, and seven in classes IV or V Five of the children were not living with both natural parents. Birth order was about average for the general population. The mean (SE) Slater's index[10] (a statistic varying between 0 and 1, measuring $\frac{m-1}{n-1}$ where m=position and n=size of sibship, with a mean of 0·5 in the general population), was 0·54 (0·07). The mean (SD) age of the mothers was 35·0 (4·5) and of the fathers was 36·7 (4·9). Daytime wetting had been present continuously from infancy in 34 instances. Associated bed wetting was found in 20 and faecal soiling in five

The trial was approved by the district ethical committee

Paediatric assessment. All children were seen with a parent by one paediatrician (SRM). A full clinical history was taken before the child was physically examined. A sample of urine was collected for examination and culture. Intravenous urograms were taken in 42 children and a voiding cystourethrogram in 41 (all those with previous or present urine infection had both investigations).

In addition, all the children had urine samples checked at monthly intervals, at the time of any suspicious symptoms, as well as a few days after the conclusion of a course of antibiotics. (Any appreciable bacteriuria was eradicated with a three day course of antibiotics. Recurrence of infection was treated similarly and then by prolonged low dose prophylactic treatment, usually in the form of nitrofurantoin 25 mg every night).

Of the nine boys, two were considered to have had previous urine infections. None had bacteriuria during the study that required chemotherapy Of the 35 girls, 21 were considered to have had previous urine infections and 12 had one or more episodes of infection during the study and eventually required continuous prophylactic treatment

Of the 42 intravenous urograms, 35 yielded normal results. Four showed duplex systems on one side, two entering the bladder by two ureters and two by a single ureteric opening. Two children had mild clubbing of the calyces and cortical thinning, suggesting 'pyelonephritis', which was bilateral in one and unilateral in the other. One child had what seemed to be a dysplastic kidney on one side.

Of the 41 cystourethrograms, 25 yielded normal results. Twelve showed vesicoureteric reflux, which in five was minor (grade 1), but four showed grade 2 and three grade 3 reflux In all but two (which showed bilateral grade 2 reflux) the reflux was unilateral. Three cystograms showed paraureteric bladder diverticula and one a mildly trabeculated bladder.

Psychological assessment. When the preliminary paediatric assessment had been completed the mother and child were seen by a psychologist (SH), who described and explained the trial. The contingent alarm that went off when wetting occurred might help the child to recognise when the bladder was full The non-contingent alarm that went off from time to time, irrespective of wetting events, would remind the child to use the toilet and might help build up more regular toilet visiting habits. It was arranged for child and parents to chart wetting and soiling by checking four times a day and to note visits to the toilet for a month before treatment was started. The psychologist told the mothers that she would keep in touch by home visits and, when possible, by telephone as well as during their regular visits to the outpatient clinic. General advice was given about personal hygiene, the use of bactericidal powders and deodorants, and the need to empty the bladder regularly, particularly at school (free access to toilets was facilitated by contacting the teachers)

About 10 days later the psychologist interviewed mothers at home, asking about features of the wetting problem and home circumstances. The Rutter A scale was used, which provides a standard set of questions for asking mothers about the psychological adjustment of their children.[4] Tape recordings of this part of the interview were made. Mothers completed a self administered dependency questionnaire[5] concerning the child and a Leeds scale with regard to their own psychiatric state.[6] Children were seen on their own to explain the procedure. Subsequently, class teachers were asked to complete the Conners teachers questionnaire.[7] They were also asked to fill in one of these scales for the next child of the same sex on the class register for us to use as a control subject. Mothers of these control children were asked to complete Rutter A, Leeds scale, and self administered dependency questionnaire forms. When children and parents had agreed to try using the alarm at school as well as at home teachers were asked to allow the child to leave the class when the alarm sounded, under the pretext of having to take medication, so that they could change and use the toilet. A month after the initial contact and immediately before using the alarm the child was brought back to hospital for a video recorded observation session as previously described.[8] This provided information about the circumstances surrounding the occurrence of wetting and urges to use the toilet as well as an estimate of maximal functional bladder capacity. (Halliday S, Berg I, Meadow SR. In preparation.)

Reliability of ratings of disturbance. There was complete agreement in 70% of instances when tape recorded interviews with mothers were rated for the presence of psychiatric disturbance in the children by three independent researchers (IB, SH, and Dr G Richardson). Discrepancies of more than one point on a three point scale (normal, borderline, or disturbed) only occurred twice. There was total disagreement between the researchers on only three times. Agreement between pairs of researchers ranged between 74 and 84%.

The alarms. The two alarms (Headingley Scientific Instruments*) were identical in appearance and were worn in the same manner. A flat plastic wetting sensor, silvered on one side, was attached to underpants by sticking plaster. Wires led from the sensor to a small flat box, which contained the alarm mechanism, worn on a belt or in a pocket. When the buzz occurred, because urine had come into contact with the sensor in the case of the contingent alarm or automatically in the case of the non-contingent alarm, the alarm could be turned off by unplugging the lead. Plugging the alarm in again reset the device. The child was instructed to go to the toilet to pass water when the alarm went off, to change any wet pants, and then reset the buzzer.

Compliance measures. A calibrated capillary tube containing mercury was fitted inside the box worn by the child. The mercury level rose at a constant rate when the alarm device was switched on, taking 100 hours to reach the end of the tube. Its position was recorded two weeks and one month after treatment began.

Quota allocation system. After wetting events had been recorded for a month without any treatment (the initial four weeks baseline period) children were randomly allocated to one of the two types of alarm. This was achieved using a quota allocation system,[9] allowing for sex, age group (5–8, 9–12, and 13–16 years), type of daytime wetting (primary or onset), associated nocturnal enuresis, associated soiling, frequency of diurnal enuresis (up to twice a week, three to six times a week, or daily) as well as psychiatric disturbance (definite, borderline, or none). A secretary carried out the allocation and the research workers were not told which type of alarm the child was using. Any device that failed to function satisfactorily was replaced by the secretary so that the psychologist and paediatrician remained in ignorance of the type of alarm allocated.

Criterion of success. Success was taken to be six consecutive weeks without daytime wetting. When wetting continued treatment with the alarm was stopped after three months and management was considered to have been a failure The only exception was when a urinary tract infection had been found and treated. An additional fortnight using the alarm was then allowed on each occasion infection occurred

Assessments after treatment. Within a month of stopping treatment Rutter A scale, self administered dependency questionnaire, Leeds scale, Conners teachers questionnaire, and the observation under water load conditions were repeated. Recording of wetting events was stopped. Outcome was assessed one month after stopping treatment.

Relapses. Two consecutive days on which day wetting occurred was considered a relapse. When this happened the family was asked to arrange for the alarm to be used for a week.

Follow up. A questionnaire, seeking information about wetting events, voiding habits, occurrence of urine infection, and the child's behaviour and health, was sent to parents by post at three and six months and one and two years after completion of treatment. (The questionnaire is available on request from the authors)

Results

Over the four week baseline period the mean (SD) number of daytime wetting events was 38 (20). The mean (SD) functional bladder capacity was 160 (75) ml. Assessments of psychiatric disturbance in the children by a child psychiatrist (IB) from listening to tape recordings of interviews with mothers conducted by the psychologist suggested that 11 children (25%) were definitely, and six possibly, disturbed emotionally On the Leeds scales, which estimate adult psychiatric disturbance, mothers of the daywetting children were found to have a mean (SD) score of 3·8 (3·7) (n=38), which was significantly higher than that of the mothers of controls, which was 2·2 (2·0) (n=34) ($p<0{\cdot}02$). Their mean (SD) A score of 4·1 (3·5) did not differ significantly from that of the controls, which was 3·5 (2·6).

No significant differences emerged between day wetters (n=44) and controls (n=34) on the four subscales of the self administered dependency questionnaire concerned with dependency of child on mother. There was evidence from the Conners teachers questionnaire that the 42 day wetting children showed more disruptive behaviour (factor I mean (SD) 0·2 (SD 0·4), inattentiveness (factor II mean (SD) 0·7 (0·7)), and overactive restless behaviour (factor IV mean (SD) 0·8 (0·7)) than the 30 controls (factor I mean (SD) 0·1 (0·1), $p<0{\cdot}05$; factor II mean (SD) 0·3 (0·4), $p<0{\cdot}01$; and factor IV mean (SD) 0·4 (0·4), $p<0{\cdot}01$). A significant excess of antisocial behaviour was evident in 22 day wetters tested on the Rutter A antisocial subscale (mean (SD) 1·8 (2)) compared with 19 controls (mean (SD) 0·5 (0·8), $p<0{\cdot}01$). No significant differences in neurotic behaviour between daytime wetters and controls emerged.

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None of the measures made before the start of treatment revealed any significant differences between children in the contingent (n=22) and the non-contingent (n=22) alarm groups. (Analyses of variance were used for comparisons of quantitative variables and Fisher's exact tests for looking at qualitative variables; $p<0{\cdot}05$ was taken as the significance level).

Immediate response. Five children, three with the non-contingent and two with the contingent alarm, dropped out of the study during the first week in which they were supposed to use the alarm. There were 13 successes with the non-contingent alarm, a 59% success rate if the three initial dropouts are counted as failures and a 68% success rate if these dropouts are disregarded. There were 16 successes with the contingent alarm, success rates of 73% and 80%, respectively The greater success rate of the contingent group, whether dropouts were considered failures or not, did not reach significance using Fisher's exact test Of the total group of 44, 29 (66%) became dry, five (11%) dropped out, and 10 (23%) were still wetting during the day at the end of the trial. For those who persisted with treatment for longer than a week, 75% were successes.

Considering improvement in terms of median percentage change from the degree of wetting during the baseline period, week by week during the three months of the trial, it was found that those who eventually became dry had a fully dry week by the sixth week of treatment. No child who ultimately failed achieved this (Figure).

Change in daytime wetting during the trial on a seven point scale, varying from 1=more than 85% worse to 7=more than 85% better, was used as an outcome measure in carrying out a multiple regression analysis, using age of child, social class, compliance with treatment, history of urinary tract infection, and baseline day wetting as predictors. A stepwise method was employed. The only significant predictor of outcome was severity of day wetting in the month before treatment, particularly the number of wetting events that were recorded by the third week of the baseline period ($F=12{\cdot}1$, $p<0{\cdot}001$, $r=0{\cdot}5$). When improvement was equated with 75% less wetting during the trial, and 30 wetting events by week 3 of baseline assessment was called 'severe wetting', then 16 of 20 'less severe' cases improved and nine of 19 'severe' cases improved; this difference was significant ($p=0{\cdot}05$, Fisher's exact test two tailed).

The mean (SD) number of weeks needed to reach the remission criterion—that is, six consecutive weeks of being dry by day—was 18 (8), with no significant difference between treatment groups. Most of the children complied with the instructions to use the alarm; only four children failed to show at least 100 hours of alarm use (as verified by the mercury column used to estimate compliance) in the first month of using the alarm. None of the scores on the various scales used to estimate psychiatric problems in mothers or children changed significantly in the day wetters or controls after treatment,

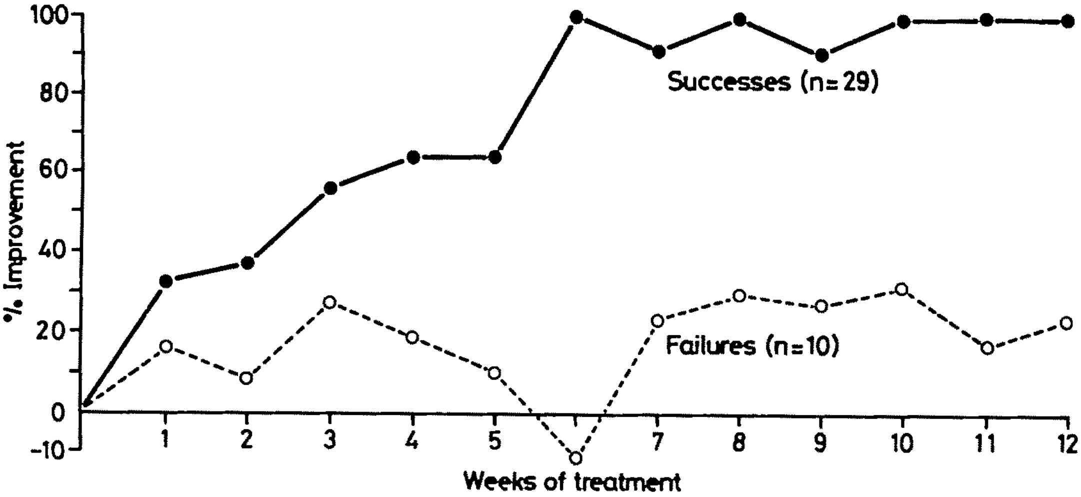

Figure *Median percentage change in wetting from baseline treatment period over three months in 39 children with daytime wetting treated with an alarm* taking the groups as a whole. The only exception was a significant fall in the assistance subscale of the patient on the self administered dependency questionnaire after treatment (mean decrease 0·9, $t_{corr}=2{\cdot}3$, $p<0{\cdot}03$, from a pretreatment average (SD) of 7·5 (2·7), $n=44$) When those who successfully responded to treatment were looked at separately, however, not only was there a significant fall in the assistance subscale of the questionnaire (mean fall 0·9, $t_{corr}=2{\cdot}1$, $p<0{\cdot}05$) but scores on factors I (mean fall 2·0, $t_{corr}=2{\cdot}8$, $p<0{\cdot}01$) and IV (mean fall 2·0, $t=2{\cdot}9$, $p<0{\cdot}01$) of the Conners teachers scale also showed significant reductions In those who failed to respond to treatment numbers were small but no change in assistance subscale of the self administered dependency questionnaire was evident, factor I of the Conners teachers questionnaire showed an increased score (mean 1·0, $t_{corr}=2{\cdot}5$, $p<0{\cdot}03$), and the mothers' mean Leeds D scale score declined significantly (mean fall 2·1, $t_{corr}=2{\cdot}9$, $p<0{\cdot}02$)

Ratings of childhood disturbance calculated by the psychiatrist from recordings of interviews with mothers carried out by the psychologist suggested that seven of the children were definitely and seven possibly disturbed psychiatrically Of the 25 children who were not considered to be disturbed before treatment, 24 showed no change Six of the 14 who had some degree of disturbance beforehand remained unchanged, whereas the other eight had improved, with five being completely free from disturbance Treatment groups did not differ in these respects.

The mean (SD) functional bladder capacity after treatment was 176 (108) ml Change from mean bladder capacity measured before treatment began was not significant Considering only those children who had no urinary tract infections while using an alarm, however, there was a significant rise in mean (SD) bladder capacity with treatment (before treatment 146 (68) ml and after treatment 180 (107) ml, $p<0{\cdot}01$).

Follow up. The 29 children who responded successfully to treatment were followed up after six months. Two were found to have relapsed, so that 27 (93%) were still free from day wetting. After a year only 25 could be reviewed and 19 (76%) remained dry by day. Twenty two children were followed up at six months and one and two years after treatment. Of these, 18 (82%) had remained free from day wetting throughout, although one had had a temporary relapse during a bout of influenza.

Discussion

The findings of the trial were encouraging in that about two thirds of children with daytime wetting responded satisfactorily to either alarm. This is a considerable improvement on previous methods of treatment. Our previous investigation showed no significant difference between the drug imipramine and a placebo, in the management of diurnal enuresis, with only a fifth of the children becoming reliably dry.[3] There is some evidence that mothers of daytime wetters attribute the problem to their child's reluctance to go to the toilet in time,[11] and this may well be a factor,[8] so that effectiveness of the non-contingent alarm may lie partly in persuading the child to empty the bladder regularly when it is not too full and also doing this without prompting by parents.

The non-contingent alarm is simpler to use than the contingent one. The finding that it worked just as well as the contingent one, within the limits of a reasonably sized clinical trial, suggests that little would be lost in using it routinely for all children with diurnal enuresis. Our current clinical practice is to use a non-contingent alarm in the form of an inexpensive commercially produced timer, which is less cumbersome and more robust than the alarm used in the trial. Staff trained in using such a non-contingent alarm provide the family with the sort of guidance and support that was given during the trial. It is also arranged for the school to permit the child to leave the classroom to use the toilet more easily than is normally allowed. (During the trial no adverse reports of using the alarms in school were received from teachers.)

The design of the study did not permit the conclusion that the use of the alarms per se brought about improvement in the day wetting. The improvement might possibly have been due to placebo effect and support given by the researchers. This seems rather unlikely as poor results were obtained in our previous drug trial at the same clinic[3] and successful outcome was not related to frequency of contact with the psychologist in the investigations reported in this paper (None of the failures had less than three or more than six visits (mean 4·1 visits) and the successes had between one and five visits (mean 3·4 visits).

It was encouraging that only about 10% of patients dropped out, rather better than when bedwetting was treated with a pad and bell.[12] Although about half of children did not wear their alarm all the time, particularly at school, this did not seem to influence the results, and compliance measured in terms of hours of usage was generally good. The finding that severity of daytime wetting was identified as the principal antecedent of poor response to treatment was not unexpected. The failure to find any connection between relief of daywetting and improvement of bedwetting is in keeping with previous work.[2,3] What seemed to be an effect of urinary tract infections in preventing a significant increase in the maximum functional bladder capacity after treatment was interesting and requires further investigation.

The high incidence of urine infection, particularly in the girls, fitted in with our previous studies of children with day time wetting.[11] It seems that wetting during the day predisposes to infection and that infection itself makes bladder control more difficult and day time wetting more likely Bladder detrusor instability is more pronounced when the urine is infected Thus investigation of urine for infection and then elimination of that infection is an integral part of the management of day time wetting The high incidence of minor radiological abnormalities of the urinary tract was surprising The abnormalities themselves, however, were probably not responsible for the wetting The radiological abnormalities seemed to be more in the nature of evidence of functional bladder disturbance, perhaps signifying that anatomical and functional development of the urinary tract went slightly astray earlier in life.

The high level of psychiatric problems in the sample was not surprising as this is a well established feature of diurnal enuresis.[13–15,1] The finding that mothers of daywetting children were more likely to be depressed, as indicated by high scores on the Leeds scale, was interesting as measures of maternal psychiatric state have not usually been used in previous studies.[16] Also the use of a dependency scale provided new information about daytime wetters. It is interesting that there was in fact no evidence that children who wet by day were deviant in their dependency on mother. It is also noteworthy that the psychiatric disorders of the day wetting children were more in the nature of antisocial than neurotic disturbance by comparison with previous studies of a similar kind,[3,11] considering the preponderance of girls in the sample of cases Changes in the average scores on the various scales after treatment provide some indications of possible processes involved in remission. The increased independence of the children, who were relieved of daytime wetting, in respect of 'task oriented' dependency[5] and the reduction in antisocial conduct suggest that the children who recovered became more cooperative and were more prepared to look after themselves. The small number of failures in treatment make comments about changes in questionnaire measures in that small group difficult.

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Urinary nitrite in symptomatic and asymptomatic urinary infection

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SUMMARY The dipstrip test for urinary nitrite is fairly unreliable in symptomatic urinary infections and only 104 (52%) of 200 symptomatic children with urinary infection attending an emergency department had a positive result. The test yielded positive results, however, in 83 of 100 outpatients with largely asymptomatic urinary infection attending a follow up clinic because of known predisposition to urinary infection. This difference was highly significant

The finding of urinary nitrite is highly specific for urinary infection and only 1% of 300 uninfected urine specimens gave a positive result.

After addition of a broth culture of *Escherichia coli* to sterile urine incubation at 37°C for four to six hours was required before the nitrite test yielded positive results. This suggests that frequency of micturition in urinary infection reduces the reliability of the nitrite test. On the other hand, the use of overnight, first morning urine specimens may further improve the sensitivity. If nitrite testing is used for screening for urinary infection at home, however, patients should be warned not to rely on a negative result in the presence of symptoms of urinary infection.

The reliability of the nitrite test for urinary tract infection (UTI) has been investigated by several workers, most of whom have concluded that false positive results were rare and that the test had a high specificity for UTI. The sensitivity of the test, defined as the proportion of infections with positive nitrite reactions, has been reported to be low (21–59%) by some authors[1–7] and high (80–93%) by others.[8–12] Those reporting low sensitivity advise against the use of the test in screening patients at risk of UTI, while it is advocated by those who have found high sensitivity.

The nitrite test is based on the ability of most infecting bacteria to reduce dietary derived urinary nitrate to nitrite The observation that bacteria that reduce nitrate require incubation in urine for some hours before a test for nitrite yields a positive result was consistent with the finding that a higher yield of positive results is obtained from samples collected early in the morning, from patients with infected urine, than from samples collected at random during the day.[12] These observations suggested that frequency of micturition in patients with UTI could be a possible cause of false negative nitrite reactions. False negative results, however, were uncommon during outpatient follow up of well patients prone to UTI. If the nitrite test had a high sensitivity in such asymptomatic patients it could be useful in screening patients at risk of UTI. Screening at home could then enable early detection and treatment before symptoms arise.

This paper examines the sensitivity of urine nitrite tests in patients attending an emergency department with symptomatic UTI compared with a group of patients with UTI but without symptoms An explanation is offered for the observed difference based on the nitrite generation time in bladder urine.

Patients and methods

Two hundred patients, aged 3 weeks to 16 years (mean 5·9 years), whose urine cultures grew $\geqslant 10^5$ bacteria/ml in pure growth of a single organism from midstream or suprapubically aspirated specimens, attended the emergency department of our hospital between January and September 1985. All these patients had symptoms that led to attendance at the emergency department and to urine culture. As complaints of frequency, dysuria, and other symptoms are dependent on individual, subjective factors, however, we have not attempted to analyse the symptoms that led to the urine test. Patients who had only plastic bag specimens were excluded. Suprapubically aspirated specimens were obtained from 17 of these children who were less than 3 years of age (mean 7·8 months) and in all the number of organisms was $\geqslant 10^5$/ml

Between October 1984 and September 1985, 100 outpatients aged 3 to 14 years (mean 9·0 years) attended a follow up clinic and were found to have $\geqslant 10^5$ bacteria/ml in midstream urine specimens These patients were being followed because of known predisposition to UTI and their urine tests were performed during regular follow up visits when most patients were asymptomatic

Ninety three of these 100 patients with UTI who attended the follow up clinic were investigated by micturating cystography and either intravenous urography or ultrasonography. Fifty three (57%) had lesions causing urinary stasis (44 vesicoureteric reflux, three bladder diverticula, four neuropathic bladder, and two partial pelviureteric obstruction). The other 40 had no radiological abnormalities

The results of nitrite tests were also ascertained in midstream urine samples with low or zero bacterial counts ($<10^4$ bacteria/ml) from 200 patients attending the emergency department and 100 patients attending the follow up clinic to determine the frequency of false positive results in uninfected urine.

Urine specimens were collected on arrival in the emergency or outpatient departments and tested immediately. No attempt was made to obtain first morning specimens. Urine nitrite tests were carried out using Boehringer Mannheim Nitur-test dipstrips and were read by laboratory medical scientists. Nitrate was not added to the specimens.

To determine the time required to generate nitrite in urine at body temperature a broth culture of *Escherichia coli* was added to 20 sterile urine samples negative for nitrite to produce a final organism concentration of 10^5/ml. Samples were then incubated at 37°C and tested every 30 minutes for nitrite reaction. When a positive nitrite reaction occurred the sample was cultured on dipslides (labslides, Bunzl Medical and Laboratory Products).

Results

Of the 200 symptomatic patients attending the emergency department with $\geqslant 10^5$ bacteria/ml in midstream or suprapubically aspirated urine specimens, 104 (52%) had a nitrite test that yielded a positive result. Only seven of the 17 suprapubically aspirated specimens from infants gave a positive result. Of the 100 outpatients with $\geqslant 10^5$ bacteria/ml identified in midstream urine specimens obtained on routine clinic visits, 83 (83%) had a nitrite test that yielded a positive result. The difference in the proportion of infections positive for nitrite between the symptomatic patients attending the emergency department and the largely asymptomatic patients attending routine outpatient follow up was highly significant ($\chi^2=25\cdot98$, $p<0\cdot0001$).

The distribution of nitrite reactions according to the infecting organism is shown in the Table. The absence of any nitrite positive reactions in streptococcal UTI reflects the known absence of the nitrate reductase enzyme in these organisms.[5 8]

When 10^5 *E. coli*/ml were added to 20 sterile urine specimens and incubated at 37°C one specimen became nitrite positive by four hours, 10 specimens by four and a half hours, 16 by five hours, and 19 by six hours. One sample still had no detectable nitrite at six hours All 20 urine samples supported growth of the organisms as shown by culture at the end of the incubation.

To assess whether anatomical conditions with urinary stasis led to increased sensitivity of the nitrite test, the sensitivity of the test in infected patients with radiological abnormalities was compared with the sensitivity in those with normal urinary tracts. Of the 53 patients with radiological abnormalities attending follow up clinic, five had streptococcal UTI. As streptococci do not reduce nitrate these five patients were excluded from the analysis. Of the remaining 48 patients, four (8%) had tests that produced false negative results. Of the 40 patients with radiologically normal urinary tracts, attending follow up clinic, one had a streptococcal UTI and was excluded, and five (13%) of the remainder had tests that gave false negative results. Clearly, the difference was not significant ($\chi^2=0\cdot11$).

Of 200 urine specimens with $<10^4$ bacteria/ml from patients attending the emergency department, two had tests that yielded positive results, and of the 100 patients with low bacterial counts attending follow up clinic, only one had a positive result. Of these three patients whose tests apparently yielded false positive results, one had recently begun treatment with antibiotics.

Table *Nitrite test results according to infecting bacteria*

Bacteria	*Emergency department patients*		*Follow up clinic patients*	
	Total	*Nitrite positive*	*Total*	*Nitrite positive*
Escherichia coli	165	93	87	77
Streptococcus spp	5	0	6	0
Staphylococcus spp	12	3	2	2
Klebsiella spp	5	2	2	1
Proteus spp	9	6	1	1
Pseudomonas spp	4	0	1	1
Citrobacter spp	0	0	1	1
Total	200	104	100	83

Discussion

The findings of this study show a considerable difference in the sensitivity of the urine nitrite test as an indicator of UTI in patients with symptomatic and asymptomatic infections. This difference could explain the wide variation in sensitivity reported in the published reports. Because of the high frequency of negative results of nitrite assay in patients with symptomatic UTI, the value of the test is limited to those in whom a positive result is obtained. More reliability can be placed on the sensitivity of the test in the follow up management of asymptomatic patients, although 17% of such infections were not detected.

Kass has shown that urine cultures with $\geqslant 10^5$ bacteria/ml are reproducible evidence of infection in 80% of asymptomatic women.[13] Although the criteria of UTI in children are not so well defined, cultures of a single organism in numbers of $\geqslant 10^5$/ml in midstream urine samples are generally regarded as sufficient evidence for diagnosis of UTI. As in adults, however, a small proportion of such cultures probably do not result from UTI but from gross contamination, and these specimens could account for some of the apparently false negative results seen in our patients.

Urine aspirated from the bladder by suprapubic puncture should normally be sterile and any number of organisms generally indicates infection In all our cases with positive cultures from suprapubically aspirated specimens colony counts of $\geqslant 10^5$/ml were obtained. These specimens were all from symptomatic infants and their lower frequency of positive nitrite reactions may be related to a shorter incubation time in the bladder.

This study confirms that incubation at 37°C of at least four to six hours is required for generation of detectable nitrite in infected urine samples, and therefore patients with a high frequency of micturition might be expected to have a high likelihood of false negative results. It is suggested that the higher sensitivity of the nitrite test in the patients attending follow up clinic was due to the infections being mostly asymptomatic and not associated with frequency of micturition.

By increasing the time that infected urine is retained in the urinary tract, lesions such as vesicoureteric reflux and bladder diverticula would be expected to be associated with fewer false negative results of nitrite tests. While there was no significant difference in the sensitivity of the nitrite test in asymptomatic patients with and without these lesions, a greater proportion of the patients attending follow up clinic had radiological abnormalities than would be expected in the unselected patients attending the emergency department. This factor may also have enhanced the sensitivity of the test in the patients attending follow up clinic

The higher sensitivity of nitrite tests in asymptomatic infections suggests that the tests could be useful in the monitoring of patients prone to UTI with structural abnormalities of the urinary tract. Weekly, or twice weekly, urine tests at home have been advocated.[8] By ensuring that only overnight, first morning urine specimens are nitrite tested by asymptomatic patients undertaking home surveillance a degree of sensitivity higher than that observed in our patients attending follow up clinic might be expected.[12]

Although we have found a false negative rate of 17% in asymptomatic patients attending follow up clinic, the findings suggest that home screening would detect at least 83% of asymptomatic UTI, allowing treatment before symptoms develop The low incidence of false positive results would not lead to unnecessary investigation of large numbers of uninfected patients. Patients undertaking home screening should be warned, however, that nitrite tests are much less reliable in the presence of symptoms of urinary tract infection.

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Vascular access for acute haemodialysis

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SUMMARY Vascular access for acute haemodialysis was required on 29 occasions in 26 children over a six year period. Comparison was made of the forms of vascular access employed, these being the Scribner shunt, the Hickman line, and percutaneous polyvinylchloride cannulae. The Hickman catheter was used to provide vascular access in 17 patients (mean age 8·8 years (range 2·5–16 years) and mean weight 25·5 kg (range 7·7–60 kg)) and allowed adequate haemodialysis to occur. Only one catheter had to be removed because of infection, and no other serious complications were encountered. These results show the superiority of the Hickman catheter as vascular access for acute haemodialysis in children.

Haemodialysis is now practised widely in the management of renal failure in children,[1–3] in spite of the problems of creating vascular access.[4] For long term haemodialysis, arteriovenous shunts—for example, Brescia shunts[5]—and internal fistulae—for example, the use of a saphenous vein loop[6]—can be created successfully using microvascular techniques. These forms of access have the disadvantage that they require between six and eight weeks to mature before they are available for use. There are, however, a number of children who require acute haemodialysis—those with acute renal failure in whom acute peritoneal dialysis is not feasible and those undergoing long term dialysis in whom there is a failure of established vascular access or peritoneal dialysis. While internal fistulae using polytetrafluoroethylene grafts may be used to provide acute access in these children, such grafts have a high incidence of thrombosis, infection, and pseudoaneurysm formation[4 7 8] For these reasons, vascular access for acute haemodialysis usually requires some form of external device

In the Manchester paediatric renal unit it had been the practice until 1981 to insert an external arteriovenous fistula (Scribner) to provide access in these children. Since that time the use of siliconised right atrial catheters (Hickman[9]) has been the preferred mode of access.

This study reviews the relative merits of these forms of vascular access for acute haemodialysis in children.

Materials and methods

A review was made of all children in the regional paediatric renal/dialysis unit (based in our two hospitals) who underwent acute haemodialysis during the period 1979–86.

A record was made of the indications for dialysis, the type of access used, the duration of dialysis, and the complications encountered. Three different forms of vascular access were employed, these being the Hickman catheter, the Scribner shunt, and percutaneously inserted venous and arterial lines (used for a small number of children only).

Hickman lines. Three different varieties of the Hickman type catheter were used, depending on the size of the patient: (1) the Broviac catheter (Evermed); (2) the Hickman catheter (Evermed); and (3) the Francis catheter (Kimal). These catheters had internal diameters of 1·0, 1·6, and 2·6 mm and external diameters of 2·2, 3·2, and 4·8 mm, respectively. All these catheters were made of silicone rubber and were of variable length, with a Dacron cuff for subcutaneous fixation and a Luer's connection at one end. These catheters were inserted in an open manner.

Under general anaesthesia a skin crease neck incision was made above the medial end of the clavicle. The catheter was inserted into either the external jugular vein, if of adequate size, or else the internal jugular, through a purse string suture of 6/0 Prolene in the side of the vein. The catheter was tunnelled subcutaneously to the anterior chest wall and the length of the catheter determined so that the tip of the catheter lay in the upper part of the right atrium and the Dacron cuff midway between the catheter entry point on the chest wall and the insertion site of the catheter into the vein. A chest *x* ray was performed on the operating table to ensure correct positioning of the catheter tip, and the neck wound was closed with Dexon The catheter was used for a single needle dialysis. Between dialyses, 3 ml of heparinised saline was injected into the catheter and a cap placed onto the Luer's connection. These catheters were also used as vascular access for sampling and infusion. Catheter entry sites were cleaned and dressed daily using Hibidil followed by dry povidone iodine spray and Mepore dressing, ensuring that no adhesive came into contact with the catheter. Bacteriological swabs of the catheter entry site were taken weekly. Catheters were removed by simple traction under sedation or a light general anaesthetic.

Scribner shunts. These shunts formed an arteriovenous fistula in which blood flowed from a cannulated artery through an external silastic tube into a cannulated vein. They were inserted most commonly in the groin, utilising the superficial femoral artery and the long saphenous vein.

Other sites used for Scribner shunts included the posterior tibial artery/long saphenous vein (two cases) and the radial artery/cephalic vein (one case).

Miscellaneous group. Two children were dialysed through percutaneously placed polyvinylchloride (PVC) subclavian lines and two through percutaneously placed PVC arterial cannulae, with the venous return being through cannulae in the external jugular and long saphenous veins.

Dialysis details. All children were dialysed using the Gambro flat plate parallel flow dialyser of the following sizes: Mini-mini Minor, 0·1 m^2; Mini Minor, 0·28 m^2; Minor, 0·51 m^2; Optima 17, 1·1 m^2; and Optima 11·5, 1·1 m^2. Paediatric lines with a total priming volume of 56 ml were used and latterly lines with a priming volume of 33 ml were used for children weighing less than 15 kg. All but one of the patients were dialysed using a Redy machine, the one exception using the AK10 Double Pump System.

Results

Vascular access for acute haemodialysis was required on 29 separate occasions in 26 children during the period studied Eight children had Scribner shunts inserted, 17 had Hickman type lines inserted, and four were dialysed through miscellaneous percutaneous lines.

The mean age of these children at the time of dialysis was 8·1 years, with a range of 9 months to 17 years, and mean weight was 26·7 kg, with a range of 7·7 to 60 kg. The distribution of age and weight in the three access groups is shown in Table 1. Scribner shunts provided dialysis flow rates of 75 to 200 ml/min, using dialysis plates of between 0·28 m^2 and 1·1 m^2. Of the 17 Hickman type lines, one Broviac catheter was inserted into a child weighing 7·7 kg, giving a dialysis flow rate of 50 ml/min, seven Hickman catheters were inserted into children weighing from 10·1 to 16·7 kg, giving a dialysis flow rate of 75 to 100 ml/min, and nine Francis catheters were inserted into children weighing more than 18 kg, giving a dialysis flow rate of 100 to 200 ml/min. The Broviac catheter used a dialysis plate of 0·1 m^2, the Hickman catheters used plates of 0·28 to 0·51 m^2, and the Francis catheters used plates of 0·51 to 1·1 m^2. The miscellaneous cannulae provided dialysis flows of between 75 and 200 ml/min, using dialysis plates of 0·28 to 1·1 m^2.

Table 1 *Mean ages and weights of the patients according to type of access used*

	Type of access		
	Scribner (n=8)	*Hickman (n=17)*	*Miscellaneous (n=4)*
Age (years)	6 0	8 8	8 5
Range	0 8–17	2 5–16	2–15
Weight (kg)	25 7	25 6	30 7
Range	8 5–49	7 7–60	11 8–52

Indications for acute haemodialysis. Acute renal failure was the commonest indication for acute haemodialysis, occurring in 21 cases. The causes of acute renal failure included seven cases of haemolytic uraemic syndrome, seven cases of peritonitis and septicaemia, five cases where acute renal failure developed in patients with chronic renal problems, and two cases of transplant failure. Of these 21 cases, acute peritoneal dialysis was attempted in four but failed due to poor drainage or subcutaneous tracking of fluid, or both. Of the remaining 17 cases in this group, acute peritoneal dialysis was thought to be inadvisable because of recent laparotomy and the presence of abdominal drains in 10 cases, previous abdominal surgery and known peritoneal adhesions in six, and anticipated bilateral nephrectomy in one.

Acute haemodialysis was performed in eight patients on long term dialysis for chronic renal failure. Five of these patients had suffered recurrent peritonitis while receiving long term peritoneal dialysis and three suffered clotting of established vascular access during long term haemodialysis. Acute peritoneal dialysis was attempted in one of this latter group but failed due to catheter blockage, while the remaining two patients had known intraperitoneal adhesions.

Dialysis details. Table 2 shows the mean number of dialyses and the time in situ of each type of access Hickman lines remained in situ longer and were used for more dialyses than either of the other two types of access.

Both the Hickman catheters and Scribner shunts were found to provide adequate access for efficient dialysis, with satisfactory blood urea clearance. In six cases (four Hickman and two Scribner) patients who were anephric or anuric were adequately maintained for a mean of 69 days (range 35 to 120 days), confirming the efficiency of dialysis using these forms of vascular access. Complications of each of the types of access were recorded and are summarised in Table 3. Ten episodes of complications were recorded with Scribner shunts, two of these being severe haemorrhage after accidental disconnection of the shunt. Surgical alteration and repositioning of the shunts was required in two cases, and in two cases ischaemic changes in the limb were noted during dialysis. Neither of these children had permanent limb ischaemia after removal of the shunt. Two Scribner shunts were problem free, but these remained in situ for only four and six days, respectively. Although five episodes of infection occurred in the group with Hickman lines, four of these were minor and readily treated with antibiotics. The fifth case of infection caused episodes of bacteraemia and the catheter had to be removed. This occurred in an immunosuppressed patient receiving prednisolone and azathiaprine, with a focus of staphylococcal infection on her leg before the Hickman catheter was inserted. The staphylococcus isolated from the leg was the same phage type as that isolated from the removed catheter Of the five surgical repositionings in this group four occurred in the same patient, in whom it was very difficult to maintain adequate flow from the catheter. The reasons for this are unknown. Few problems were encountered in the miscellaneous group, although only one of these patients had haemodialysis for more than four days.

Table 2 *Mean No of dialyses and time in situ for the three types of access*

	Type of access		
	Scribner	*Hickman*	*Miscellaneous*
Duration of access (days)	20 8	86 1	8 5
Range	2–63	1–171	3–24
No of dialyses	12 3	32 1	6 5
Range	2–36	1–88	2–18

Table 3 *Complications of the three types of vascular access employed*

	Type of access		
Complications (episodes)	*Scribner*	*Hickman*	*Miscellaneous*
Bleeding	2	0	0
Clotting	5	1	1
Inadequate flow	0	1	1
Infection	1	5	0
Limb ischaemia	2	0	0
Surgical alterations	2	5	0
Total	12	12	2
Complications/ access days (%)	7 2	0 8	5 8
No of complication free access routes	2	9	3
Mean days in situ of complication free access	5	41 5	10

Table 4 *Reasons for stopping acute dialysis through access according to type of access employed*

	Type of access		
	Scribner	*Hickman*	*Miscellaneous*
Failure of access	2 (25%)	1 (6%)	0
Establishment of permanent access/ peritoneal dialysis	0	5	0
Death	3	1	1
Recovery of renal function	3	6	2
Transplant	0	4	1

Table 4 shows the reasons for stopping haemodialysis through the vascular access. Dialysis had to be stopped because of failure of access in two cases using Scribner shunts and one using a Hickman line.

Discussion

In spite of the efficacy of peritoneal dialysis, acute haemodialysis will remain an integral part of the management of renal failure in children. Polytetrafluoroethylene grafts provide the only means of permanent internal access that can be used soon after insertion, but these grafts have a high incidence of complications. External means of access are likely, therefore, to remain the preferred route for the forseeable future. Scribner shunts have been used in the past to provide acute vascular access and provide an adequate blood flow for efficient dialysis. They have the advantage that they allow two needle dialysis. As this study has shown, however, the Scribner shunt does have some problems. In particular, the arrangement of the external loop makes the shunt prone to accidental disconnection (25% in this series), leading to severe haemorrhage.[10] In addition, the shunts are prone to clotting after repeated use (occurring in five cases (63%) in this series) and require a degree of patient immobility and often inpatient nursing care. Removal of these shunts often leads to obliteration of the superficial femoral artery, the late sequelae of which are unknown. Similar problems with Scribner shunts have been recorded in other series.[6]

By comparison, Hickman lines are fairly easy to insert and, being venous and with a Luer's connection, are less prone to accidental disconnection. These lines had fewer complication episodes per catheter day than the Scribner shunts (0·8% compared with 7·2%). While infection has often been quoted as a common problem with indwelling central venous lines, this was not reflected in this study. Factors relating to the relative lack of infective complications include the Dacron cuff on the Hickman catheter, which stimulates fibrosis and prevents the spread of infection along the track of the catheter,[6 11] the formation of an adequate subcutaneous tunnel, and the careful attention to the dressing of the catheter entry site. Similarly, clotting of these lines was not a major problem, reflecting the advantage of using silicone rubber. The low rate of thrombus formation in silicone rubber catheters compared with PVC catheters has been shown elsewhere.[12] Once in situ Hickman catheters had a fairly long life span, which avoided the need for the urgent formation of a permanent shunt and allowed time for arteriovenous shunts to mature. Other series have also described the long life span of the Hickman type catheter—for example, Vasmant *et al* reported an average time in situ of 48 days and a maximum time of five months.[13] Patients and parents were taught to care for the catheter and were often allowed home with the catheter in situ to continue haemodialysis on an outpatient basis. These catheters provided useful vascular access for other purposes, thus freeing the child from multiple venepunctures.

Other studies have confirmed these advantages of the Hickman catheter for acute haemodialysis[4 11 13 14] and its relative lack of complications compared with the Scribner shunt.[4] The chief disadvantage of the Hickman catheter is that it allows only single needle dialysis, although this problem may be circumvented using a double pump system.[6] Vasmant *et al* described the insertion of double lumen Hickman catheters, each channel having an internal diameter of 1·6 mm, in six children in whom two needle dialysis was then performed, using the Hickman catheter as the 'arterial' line.[13] In all patients except one adequate flow was obtained from the Hickman line for satisfactory dialysis. The type of catheter used (Broviac, Hickman, or Francis) was dependent on the size of the patient and the desired flow, a point emphasised by Mahan *et al*, who found that the 1·6 mm diameter Hickman line did not provide adequate flow for dialysis in children bigger than 13 kg.[4] In this study a child who weighed 16·7 kg was successfully dialysed through a similar catheter. It is recommended that the Francis catheter, with an internal diameter of 2·6 mm, should be used for children weighing more than 15 kg.

The miscellaneous group had dialysis performed through assorted percutaneous cannulae in very sick children. While these provided adequate short term access in this and other series,[15] they are unsuitable for longer term use.[14] Even in these sick children it is suggested that the Hickman catheter (which may be inserted in the intensive care unit) is the preferable form of vascular access.

Conclusions

It is concluded that the Hickman right atrial catheter is the preferred means of vascular access for acute haemodialysis in children, because of its ease of insertion, relative lack of complications, and durability. It provides an adequate route for efficient dialysis provided that the correct size of catheter is employed, based on the patient's weight. In these respects it is superior to both the Scribner shunt and to percutaneously placed PVC catheters.

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Cot deaths, stillbirths, and the probation service: a potentially recognisable at risk group

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SUMMARY Families of clients under the care of the probation service are at significantly higher risk of experiencing a cot death or a stillbirth than the general public. Pregnant women in the immediate families of clients under the care of the probation service should be identified to health service personnel involved in their antenatal and postnatal care in an effort to avert unnecessary deaths.

The present study was undertaken to ascertain whether sudden infant death syndrome was more common in infants whose parents were under the care of the probation service. This followed a casual enquiry from a probation officer to one of us (EP) for information regarding cot death as several cases had been noted within the local service over the preceding year.

The work of the probation service is predominantly with offenders and their families. Home Office probation statistics for 1984 revealed that nationally some 147 000 people were under the care of the probation service on the census day (31 December 1984). Of those being supervised, 82% were men, 53% of whom were aged between 17 and 29 years. About half the women being supervised were also aged between 17 and 29 years. The types of offences committed by those beginning probation have changed little over the last five years, with Home Office statistics revealing that roughly a half of the clients had been found guilty of theft, with another 7% convicted for violence against the person.

A search of the publications revealed little information about the health of persons on probation. One study suggested that as many as 10% of clients of the probation service may be receiving psychiatric treatment.[1] A sizable number of youth who enter the judicial system each year may be at risk of psychiatric disability[2] A physical examination of 233 juvenile delinquents on a comprehensive probation programme found most in poor health.[3] No studies could be found concerning the outcome of pregnancies among clients on probation nor about the health of the clients' children.

In England and Wales there are about 1300 'sudden infant deaths' in the first year of life,[4] representing about one third of the annual total of deaths after the neonatal period. A recent multicentre study showed evidence of an increased risk of infant death in lower social class families, with more children having more family problems and living in less satisfactory housing.[5] Family and community factors associated with potentially preventable infant deaths were identified by Taylor and Emery.[6] These included domestic, financial, and housing problems, parental health, parental intelligence and competence, and family circumstances.[6] Studies of women addicted to opiates have shown high incidences,[7] barbiturates also having been implicated.[8] The suspicion of filicide (child homicide by either parent) may be a major factor in between 2% and 10% of unexplained cot deaths.[9] [10] Attempts have been made to create a scoring system to identify infants at risk of 'unexpected death', using combinations of various factors present at the birth of the child. Their use, however, remains controversial, the multicentre study acknowledged the discriminatory power of the at birth risk scoring system of Carpenter *et al*[11] but remarked on its low sensitivity and specificity.[5] The cost-benefit ratio of scoring systems also remains an area of debate.[12]

A client group comprising those on probation has an undoubted preponderance of the factors associated with high incidence of cot deaths. High risk at birth scores could be expected from such mothers.

Methods

The initial study was conducted in the Cleveland probation service in April 1985. All probation officers in the service were asked to review their records to provide details of the number of births and cot deaths that occurred to female clients on probation or to the wife, common law wife, or girlfriend of a male client on probation during the calendar year 1984.

After the initial results a second survey was deemed appropriate; four other probationary areas were approached in November 1985 to obtain similar basic data to the initial study, including the number of stillbirths for the calendar year 1985. A standardised simple questionnaire was circulated to all probation officers for completion.

Results

Three of the four probation services responded to the second survey. Results from both surveys are shown in Tables 1 and 2. Five cots deaths were identified from Humberside, Northumberland, and Durham, with an overall rate of 13·5 per 1000 births (one in 73 live births). Numbers of stillbirths were returned from the initial survey, though they were not requested; the second survey specifically requested stillbirth figures. The initial Cleveland survey revealed a stillbirth rate of 44 per 1000 births and the second survey a rate of 24 per 1000 births.

Table 1 *No of births, cot deaths, and stillbirths occurring to female clients or to wives, common law wives, or girlfriends of male clients on probation in four probation districts*

Probation district	*Year*	*Births (estimated)*	*Cot deaths*	*Stillbirths*
Humberside	1985	113	4*	3
Northumbria	1985	185	1	3
Durham	1985	72	0	3
Cleveland	1984	68	3	3†
Total		438	8	12

*One was a filicide
†Information received but not requested

Table 2 *Rates/1000 births of cot deaths and stillbirths for clients on probation compared with national figures*

	Rates/1000 births		
	Probation survey	*National (1984)*	*Relative risk*
Cot death	18 2*	1 95	9 4
Stillbirth	27 4**	5 7	4 8

*χ^2 (with Yates's correction)=50 1, p<0 001 (excluding Cleveland χ^2=19 5, p<0 001)
**χ^2 (with Yates's correction)=34 5, p<0 001 (excluding Cleveland χ^2=20 7, p<0 001)

Discussion

Families of clients under the care of the probation service are at significantly higher risk of experiencing a cot death or a stillbirth than the general public. Indeed these results suggest that about one in 20 pregnancies in the families of clients under the care of the probation service might have such a fatal outcome. Reasons for this are likely to be multifactorial, with physical, social, and psychological factors all probably implicated.

Confidentiality is respected about being 'on probation', and health service workers will not usually be aware that a person is on probation. At present in Cleveland no extra health service input is aimed directly at this client group. On the other hand, the probation service seems to see a high risk client group for which the need for the intervention of the health service would seem to be great. Pregnant women in the immediate families of clients under the care of the probation service should be notified to the health service personnel involved in their antenatal and postnatal care in an effort to avert unnecessary deaths.

Thanks must be extended to the chief probation officers, without whose cooperation the study would not have been possible, thanks are also due to the individual probation officers for their work in supplying the data

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Outbreak of cephalosporin resistant *Enterobacter cloacae* infection in a neonatal intensive care unit

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SUMMARY *Enterobacter cloacae* resistant to third generation cephalosporins emerged rapidly during an outbreak of serious infections due to this organism in a neonatal intensive care unit where ampicillin and gentamicin were used as first line antibiotic treatment. Organisms resistant to cephalosporins were isolated from 12 infants, six of whom developed systemic infection. Two infants died. Isolates of *E. cloacae* from four of five infants treated with cefotaxime showed a loss of sensitivity to this antibiotic during treatment, but in the three infants who survived sensitive organisms were again isolated after treatment had stopped. Stopping treatment with the cephalosporins, closure of the unit to new admissions, and strict cohorting of colonised infants resulted in a prompt end to the outbreak.

This outbreak suggests that the routine use of third generation cephalosporins for suspected sepsis may be inappropriate in the presence of a large reservoir of organisms with the potential for rapidly developing resistance. Routine bacteriological surveillance, however, might permit their use on a rotational basis.

Infection is common in babies in neonatal intensive care units. It may be overwhelming but early signs are largely non-specific and babies from such a population often receive broad range antibiotics before the results of cultures are available. The combination of an aminoglycoside and a penicillin is widely used [1] Recently, the emergence of gentamicin resistant organisms and the potential problems of aminoglycoside ototoxicity, nephrotoxicity, and poor penetration into cerebrospinal fluid (CSF) has led to third generation cephalosporin monotherapy being advocated for routine first line treatment.[2] We describe our experience of third generation cephalosporins in a unit that has continued to use ampicillin and gentamicin as first line treatment. We suggest that the routine use of third generation cephalosporins as first line treatment for suspected infection in neonatal intensive care units may be inappropriate.

Background

The regional neonatal intensive care unit, Liverpool Maternity Hospital, admits between 450 and 500 babies each year. Roughly 30% weigh less than 1500 g at birth and about 30% are outborn.

Handwashing with a chlorhexidine solution followed by application of an alcohol rub is carried out before every infant contact. Gloves are worn during nursing procedures and napkin changes. Routine infection surveillance includes culture and sensitivity testing on daily specimens of tracheal aspirate from intubated babies and weekly rectal and superficial swabs from all babies. A full infection screen, consisting of superficial swabbing and urine, CSF, and blood cultures, is carried out on all outborn babies on admission.

The combination of ampicillin and gentamicin has been used as the standard initial treatment of suspected infection for five years. Over 95% of babies receive broad range antibiotics at least once during their admission.

Laboratory methods

Standard methods and media were used for isolation of organisms.[3] Species identification of isolates was carried out on the basis of biochemical reactions, using the API 20E system (API Products, Basingstoke). Sensitivities to selected antibiotics were determined by the breakpoint method, using Oxoid DST agar and a multipoint inoculator that produced an inoculum of 10^5 colony forming units. To incorporate antibiotics of required concentrations into the DST agar, Adatabs (Mast House, Bootle) were used. Breakpoints were 1 mg/l (low) and 4 mg/l (high) for gentamicin and 2 mg/l (low) and 8 mg/l (high) for cephalosporins. The plates were incubated at 37°C overnight. Isolates were considered resistant to gentamicin or to the tested cephalosporin if growth was noticed on plates containing 4 mg/l or 8 mg/l of respective antibiotic.

Clinical observations

The pattern of colonisation in this unit is one of fluctuating numbers of infants colonised with *Staphylococcus epidermidis*, yeasts, and strains of *Pseudomonas, Klebsiella, Serratia,* and *Enterobacter.*

From March 1985 increasing numbers of isolates of gentamicin resistant *Staph. epidermidis* resulted in the use of cefuroxime for infections caused by this organism. Infection with *Staph. epidermidis* accounts for most blood cultures that produce positive results and cefuroxime therefore became the third most commonly used antibiotic in the unit. Concurrent with this increase in use of cefuroxime routine bacteriological surveillance revealed an increasing proportion of babies colonised with *Enterobacter cloacae,* most of whom were resistant to cefuroxime. Up to the end of June 1985 all isolates of *E cloacae* were sensitive to the third generation cephalosporins cefotaxime and ceftazidime. During July strains resistant to all cephalosporins tested first occurred

Results of weekly bacteriological surveillance from 4 June 1985 to 17 September 1985 are presented in the Figure. Screening swabs were obtained from each baby on the unit every Tuesday. The total number of babies in the unit is shown with the proportion colonised with *E. cloacae* and the proportion harbouring strains resistant to cefotaxime. Resistant organisms were recovered from 12 infants on 21 occasions over an eight week period. Seven of these infants had not been on treatment with a cephalosporin at the time of isolation of the resistant strain.

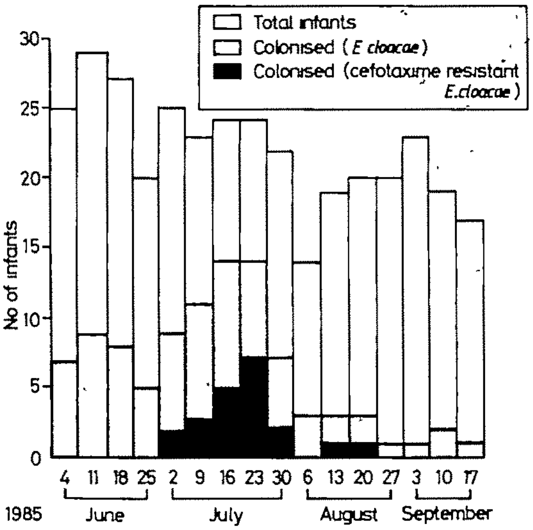

Figure *Total No of babies on the neonatal unit by weekly intervals on the days that infection screening was undertaken, showing the proportion colonised with* Enterobacter cloacae *and with cefotaxime resistant strains.*

Table *Details of infants with systemic* Enterobacter cloacae *infection initially sensitive to cefotaxime but who developed resistance after treatment*

Case No	*Birth weight (g)*	*Gestational age (weeks)*	*Infection*	*Days**
1	1840	30	BCs	7
2	1210	28	BCs, CSF	7
3	1090	28	BCs	2
4	1320	27	BCs, CSF	3

*Days after start of treatment that resistant organisms isolated
BCs=Blood cultures, CSF=Cerebrospinal fluid

During this time a cluster of serious infections with *E. cloacae* arose, with two episodes of ventriculitis and septicaemia (one episode of ventriculitis prolonged at 19 days) and four more cases of isolated septicaemia. Two infants died and two required treatment with the new quinolone ciprofloxacin. The isolates of *E. cloacae* from five of these six infants with systemic infection were initially sensitive to cefotaxime, and these five were thus treated with cefotaxime: isolates of *E. cloacae* from four revealed a loss of sensitivity to cefotaxime and to other third generation cephalosporins during treatment (Table). In the three of these four infants who survived *E. cloacae* sensitive to the third generation cephalosporins was once again isolated after exposure to cefotaxime had ceased

Infection control measures were begun and included strict cohorting of infants colonised with *E. cloacae,* stopping treatment with all cephalosporins, and closure of the unit to new admissions. Third generation resistant strains of *E. cloacae* disappeared promptly and the level of colonisation with this organism fell rapidly.

Discussion

Concern has been voiced regarding the use of gentamicin in neonatal intensive care units due in part to the increasing presence of gentamicin resistant organisms[4 5] but also to the potential hazards of ototoxicity and nephrotoxicity in an already vulnerable population; in addition, the aminoglycosides penetrate into CSF poorly. Because of these reservations the use of the third generation cephalosporins, which are relatively non-toxic and penetrate well into CSF, has been advocated as suitable first line monotherapy in neonatal intensive care units.[2]

The third generation cephalosporins are beta-lactam antibiotics that have an expanded range of antibiotic activity. Unfortunately, since their introduction several clinical problems have emerged. These include the development of resistance by the infecting organism during treatment and the concurrent development of cross resistance to most other beta-lactam antibiotics.[6 7]

A substantial proportion of strains of *E. cloacae* are resistant to the second generation cephalosporin cefuroxime and the increased use of this antibiotic for *Staph. epidermidis* infections was undoubtedly responsible for the selection of such resistant strains, with a consequent increase in numbers of infants colonised with *E. cloacae* This enlarging reservoir of *E. cloacae* thus consisted of organisms resistant to cefuroxime but sensitive to the third generation cephalosporins cefotaxime and ceftazidime. Concurrent with the increasing number of infants colonised with *E. cloacae,* however, strains resistant to cefotaxime and ceftazidime occurred.

The possibility of introduction of strains of *E. cloacae* resistant to the third generation cephalosporins from outside the unit was unlikely as all outborn babies underwent a full infection screen on admission. Furthermore, the biotypes of the isolates were identical.

Production of beta-lactamase activity may be either plasmid or chromosomally mediated, the oxime cephalosporins, cefotaxime and ceftazidime, show a high degree of stability to plasmid encoded beta-lactamase activities and are also relatively resistant to the normal amounts of chromosomally mediated cephalosporinase activities found in most wild type Enterobacteriacae.[8] If these amounts are increased, however, either by exposure of the wild type to a beta-lactamase inducer (reversible derepression) or mutation to the stably derepressed state, most third generation cephalosporins may be inactivated.[9 10] Both second and third generation cephalosporins are inducers of cephalosporinase activities in the genera *Pseudomonas, Serratia,* and *Enterobacter,* which possess chromosomally mediated inducible beta-lactamase activities (type I[11]).[7]

Both mechanisms of increased production of beta-lactamase activity may have played a part in the outbreak of infection described. *E. cloacae* resistant to the third generation cephalosporins were isolated from seven babies on routine screening swabs. At the time of isolation none had been on treatment with a cephalosporin. This observation suggests nosocomial transmission, although this cannot be proved as no information regarding serotypes was available. The biotypes of the isolates were, however, identical. As induction requires the continuing presence of the inducer, with induction ceasing when the inducer is removed, induction of beta-lactamase activity was probably not involved here; the passage of a derepressed mutant is a possibility.

In four of the five infants with systemic infection treated with cefotaxime *E. cloacae* resistant to cefotaxime and cefotazidime were first isolated after the start of treatment (Table). Once again, though the possibility of multiple strains exists, reversible induction of production of beta-lactamase activity was probably responsible for the occurrence of resistance here. This is supported by the observation that in the three infants who survived *E. cloacae* isolated after exposure to cefotaxime had ceased was again sensitive to the third generation cephalosporins.

The emergence of cefotaxime resistance during treatment with this antibiotic is recognised[5 7 12] but has been described only once before in a neonatal intensive care unit.[5] This problem is compounded because multiple drug resistance may arise simultaneously. Emergence of beta-lactam resistance during treatment with a combination of a third generation cephalosporin and an aminoglycoside has also been reported.[13]

Strains possessing inducible lactamase activities from the genera *Pseudomonas, Serratia,* and *Enterobacter* are commonly responsible for colonisation of infants in neonatal intensive care units. *E. cloacae* has been shown to have a high mutation rate [10] The common need for treatment with antibiotics, the predilection of these infants to nosocomial infection, and the rapid emergence of resistance to the third generation cephalosporins, such resistance additionally occurring during treatment, suggests that the routine use of these agents is inappropriate in the presence of a large reservoir of infants colonised with the above organisms. First line monotherapy with a third generation cephalosporin may well, however, be appropriate in the absence of such a pool of organisms. The value of the third generation cephalosporins for isolated, proven infection is undisputed. The epidemiological considerations governing the frequent use of an antibiotic blind as first line treatment for suspected sepsis must be clearly distinguished, however, from the use of an antibiotic relatively infrequently for proven sepsis. An antibiotic suitable in one context may not be suitable in the other.

Our observations once again illustrate the importance of routine bacteriological surveillance in a neonatal intensive care unit.[14] Routine surveillance also permits the introduction of alternative first line treatment regimens on a rotational basis.

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New fontanometer for continuous estimation of intracranial pressure in the newborn

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SUMMARY Intracranial pressure was estimated by a new pneumatic applanation fontanometer in babies in intensive care. A close correlation with cerebrospinal fluid pressure was found on 35 separate occasions. In 12 control babies the mean (SD) fontanelle pressure was 5·2 (2·2) cm H_2O, in eight with a hypoxic-ischaemic encephalopathy it was 12·6 (4·3) cm H_2O, and in nine with post-haemorrhagic hydrocephalus it was 10·8 (4·3) cm H_2O. In four babies monitored continuously over seven days the correlation remained good. The fontanometer enables pressure to be monitored accurately, continuously, and non-invasively in neonates at risk of raised intracranial pressure.

Several techniques for non-invasive monitoring of intracranial pressure in the newborn through the anterior fontanelle have been described over the past decade. The devices used have been either handheld or strapped to the fontanelle.[1–7] The force of application used to hold or secure these devices to the scalp, however, can distort the fontanelle and lead to a variable overestimate of the intracranial pressure.[3 4 8] Difficulty in achieving stable fixation to the anterior fontanelle has made continuous monitoring of intracranial pressure unsatisfactory There have been problems with the calibration of the devices and also with a variable zero offset in the pneumatic fontanometers. Lastly, the size of some devices has precluded their use in neonates with small fontanelles. We have designed a new pneumatic applanation fontanometer to overcome these difficulties and have compared the result obtained with direct cerebrospinal fluid (CSF) pressure measurement.

Patients and methods

The body of the fontanometer is made from a semi-flexible thermoplastic by injection moulding and measures 10 mm in diameter and 4 mm in depth. A schematic section is shown in Figure 1 and a diagram of the whole intracranial pressure measuring system in Figure 2. Three ports are provided: port 1 for gas flow in, port 2 for pressure measurement, and port 3 for gas escape. A thin, compliant polymer membrane is cemented to the perimeter of the base of the body. This initially occludes port 3 and thus a simple valve is formed. A small annular flange allows easy fixation of the body to the fontanelle by applying a thin film of industrial collodion over this flange and around the transducer body. Gas, usually air, is delivered at a constant low flow rate of 0·02 l/min, through a restrictor device, to the transducer at port 1. The gas enters the space surrounding the central escape port 3. Port 3 is initially occluded by the fontanelle pressure acting externally on the membrane, but as the air flow continues the pressure in this space rises and eventually equals the fontanelle pressure, where-

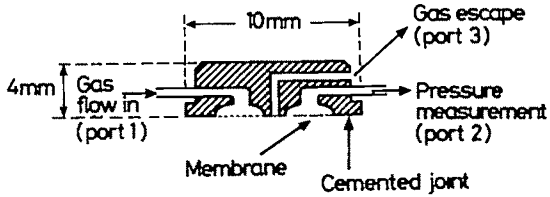

Fig. 1 *Schematic section through the transducer body (for detailed description see text).*

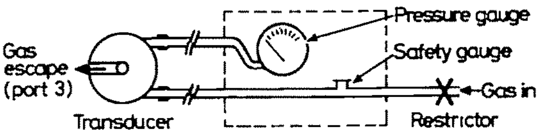

Fig. 2 *Schematic layout of the intracranial pressure monitoring system (for detailed description see text).*

upon the membrane lifts off the escape port 3, and air flows to the atmosphere. The system is now in equilibrium, and the pressure in the space surrounding port 3 is measured at port 2. Port 2 is connected by a 2 mm polyvinylchloride tube to a sensitive low pressure manometer. There is no gas flow through port 2, so the manometer accurately records the transducer pressure, thereby eliminating any zero offset. When the system is in equilibrium the pressure measured at port 2 is equal to the fontanelle pressure. Figure 3 shows the device securely applied to the fontanelle with collodion. In most babies it is possible to perform an ultrasound scan without disturbing the fontanometer. In those with a small anterior fontanelle it can be removed easily by dissolving the collodion with acetone.

The fontanometer was validated in 29 babies by comparing the result with the direct cerebrospinal fluid (CSF) pressure obtained on 35 separate occasions, 26 at lumbar and nine at ventricular puncture. The babies could be subdivided into three main groups, and their characteristics are shown in Table 1 There was a control group of 12 infants who were undergoing lumbar puncture as part of a screen for infection within the first few days of life None had meningitis or an abnormal cerebral ultrasound scan. Eight babies were studied who presented with seizures within 48 hours after birth and who were suffering from a hypoxic-ischaemic encephalopathy. CSF specimens were obtained from the eight babies for culture and the pressure measured at lumbar puncture. Nine preterm infants with post-haemorrhagic hydrocephalus were studied when CSF pressure was measured and evidence of craniospinal communication sought. In four without such communication the CSF was drained therapeutically by ventricular puncture. Direct lumbar or ventricular pressure was measured by a simple empty manometer attached to the spinal needle by a three way tap. Free flow of CSF was obtained before and after the pressure measurement. For lumbar puncture the babies were in a straight horizontal position without excessive flexion or restraint. Evidence of craniospinal communication was confirmed by Queckenstedt's test. It was assumed that with normal anatomy the lumbar and spinal subarachnoid spaces communicate freely and that the lumbar CSF pressure reflects the intracranial pressure. The oscillations of the column of CSF in the manometer tubing with heart beat and respiration were observed and a few seconds for equilibration

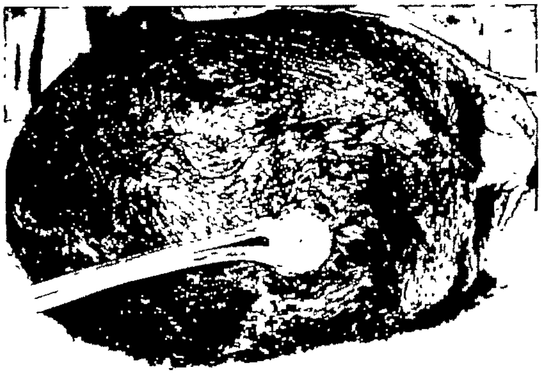

Fig. 3 *Fontanometer applied with collodion to the anterior fontanelle of a baby with a gestational age of 26 weeks*

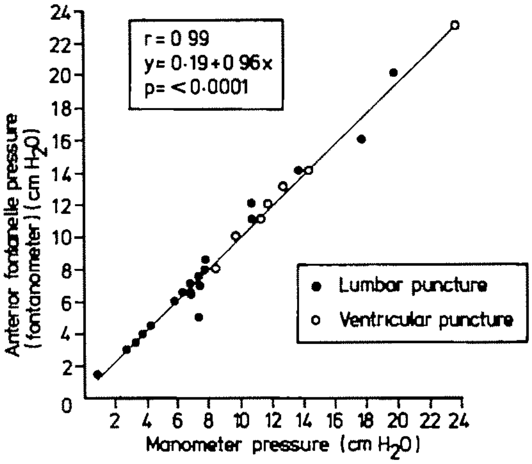

Fig. 4 *Correlation of intracranial pressure measured with the fontanometer on the anterior fontanelle with simultaneous direct measurements from lumbar puncture (n=26) or ventricular puncture (n=9)*

Table 1 *Characteristics of the three groups of babies included in the study. Values are mean (SD) [range]*

	Group		
	Control	*Hypoxic-ischaemic encephalopathy*	*Post-haemorrhagic hydrocephalus*
(n)	(12)	(8)	(9)
Gestation (wks)	33 1 (5 6) [27–42]	39 8 (1 4) [38–42]	27 3 (2 0) [24–31]
Birth weight (g)	1893 (1094) [570–3460]	3429 (326) [3115–3985]	1025 (303) [789–1673]

Table 2 *Mean (SD) [range] pressure measurements obtained in the three groups of babies by a new pneumatic applanation fontanometer and from direct cerebrospinal fluid specimens*

	Group		
	Control	*Hypoxic-ischaemic encephalopathy*	*Post-haemorrhagic hydrocephalus*
Fontanelle pressure (cm H_2O)	5·2 (2·2) [1·5–8·0]	12·6 (4·3) [8·0–20·0]	10·8 (4·3) [6·0–23·0]
Direct pressure (cm H_2O)	5·4 (2·4) [1·0–8·0]	12·9 (4·7) [8·0–20·0]	10·9 (4·4) [6·0–24·0]

allowed before the lumbar and fontanometer pressures were recorded. To investigate the reliability of the fontanometer intracranial pressure was monitored continuously over seven days in four babies without disturbing the device. The results obtained were compared with serial direct pressure measurements during that time.

Results

Cardiac and respiratory pulsations transmitted through the fontanelle to the device were seen as fine oscillations of the manometer needle throughout the period of monitoring on every occasion. Good correlation was obtained between the fontanometer estimation of intracranial pressure and the CSF pressure measured directly at simultaneous lumbar or ventricular puncture. Figure 4 shows the correlation and regression equation of measurements obtained from the fontanometer and at simultaneous lumbar or ventricular puncture on 35 separate occasions. The correlation coefficient between fontanometer and lumbar CSF measurements of intracranial pressure was good ($r=0{\cdot}98$, $y=0{\cdot}19+0{\cdot}96x$, $p=<0{\cdot}0001$, ($n=26$)). The correlation between fontanometer and ventricular measurements of intracranial pressure was also good ($r=0{\cdot}99$, $y=0{\cdot}12+0{\cdot}96x$, $p=<0{\cdot}0001$, ($n=9$)). The mean pressure measurements obtained in the three groups of babies are shown in Table 2. In the group with post-haemorrhagic hydrocephalus three babies with arrested ventricular dilatation had pressures between 6 and 7 cm H_2O, whereas the remaining six babies in this group (with progressive ventricular dilatation) had a fontanelle pressure of 10 cm H_2O or more. In the four babies studied continuously the fontanometer correlated well during the seven days ($r=0{\cdot}98$, $y=0{\cdot}14+0{\cdot}96x$, $p=<0{\cdot}0001$ ($n=12$)).

Discussion

This new applanation fontanometer when securely fixed to the anterior fontanelle of neonates with both normal and abnormal neurology gives an estimate of intracranial pressure that correlates closely with direct CSF pressure measurement No loss of reliability was found with continuous monitoring over seven days. The design overcomes the problem of zero offset, which is responsible for the unreliability of a similar pneumatic fontanometer,[6] by separating pressure measurement from the continuous gas flow. An excessive force of application and the interference with nursing procedures caused by various holding devices is avoided by fixation with collodion.[2–4 7 8] This new fontanometer is also easy to manufacture and cheap.

The mean intracranial pressure estimated by this fontanometer in the control group was lower than that quoted by workers who used other devices, handheld or strapped to the fontanelle,[1–4 7 9] but is in agreement with direct CSF pressure measurements made in a similar population.[10] Rises in intracranial pressure in babies with a hypoxic-ischaemic encephalopathy have been shown before,[3 4 7 11] and similarly we have confirmed that babies with progressive post-haemorrhagic hydrocephalus often have raised intracranial pressures,[3 4] whereas when ventricular dilatation is static the CSF pressure is within the normal range.[10] The good correlation obtained between the fontanometer and CSF pressure measurements in babies with post-haemorrhagic hydrocephalus and also in the term infants with a hypoxic-ischaemic encephalopathy enables those babies developing such problems to have continuous non-invasive pressure monitoring without resorting to invasive techniques, with the accompanying hazards.[11 12] Information about changes in intracranial pressure can now be obtained in a wide range of neonates and the efficacy of the various therapeutic manoeuvres that are commonly used to lower intracranial pressure[3 4] may now be evaluated safely and accurately.

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Thirty years ago

The nephrotic syndrome in early infancy

H McC Giles, R C B Pugh, E M Darmady, Fay Stranack, and L I Woolf (London and Portsmouth)—Arch Dis Child 1957;**32**:167–80

Thirty years ago congenital nephrosis was less clearly defined as a separate entity from idiopathic nephrosis than it is today Three infants with this disorder were described. Two were brother and sister, and their parents and paternal grandparents were first cousins The parents of the third patient, a boy, were second cousins once removed. The common clinical features included oedema, heavy proteinuria, and hypoalbuminaemia, which were noted at birth or by 6 weeks of age The serum cholesterol was markedly raised in the two siblings. All three infants died before the age of 6 months

The most striking postmortem findings were in the histology of the kidneys:

(i) The predominant lesions were in the renal tubules, especially in the cortex, with severe dilatation of the lumen and flattening or hyperplasia of the lining cells, and with vacuolation, cloudy swelling, or hyaline droplet degeneration of the epithelium Glomerular damage was minimal and thought probably to be secondary.

(ii) Microdissection of the kidneys revealed that the first part of the proximal tubule was replaced by a long and narrow neck lined by thin and flattened epithelium The remainder of the proximal tubule was ballooned and considerably wider than normal.

(iii) Doubly refractile crystalline material was found in alcohol fixed tissues (liver, bone marrow, spleen, and kidney). Its identity or importance was unknown The pattern of the aminoaciduria in all three infants and the absence of significant glycosuria, however, excluded cystine storage disease

The authors concluded that all three infants suffered from the same basic disorder and that inheritance as an autosomal recessive characteristic could well explain its occurrence. On the basis of the histological appearances the renal changes were thought to be consistent with "nephrosis", using the term in the sense of a primary tubular disorder

Comment. It seems very probable that the cases reported in this paper fall into the so called Finnish type of congenital nephrosis. While tubular dilatation is pronounced, electron microscopy has revealed that the primary defect lies in fusion of the glomerular foot processes Prenatal diagnosis is now possible in affected families by showing excess α fetoprotein in liquor amnii between 14 and 18 weeks' gestation The disease itself remains uniformly fatal unless the unfortunate infant is submitted to bilateral nephrectomy and thereafter kept alive by peritoneal or haemodialysis until a renal transplant is practicable

J H HUTCHISON

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Influence of intravenous fat emulsion on serum bilirubin in very low birthweight neonates

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SUMMARY Thirty nine very low birthweight neonates (with a birth weight of 820 to 1500 g and gestation of 27 to 34 weeks) who required total parenteral nutrition were randomly assigned to one of three regimens of administration of fat emulsion for a period of eight days. Groups 1 and 2 received the emulsion at a constant rate over 24 and 16 hours, respectively, beginning with a daily dosage of 1 g/kg and increasing daily by 1 g/kg to a maximum of 4 g/kg. Group 3 received the emulsion at a constant rate of 4 g/kg a day over 24 hours. Plasma concentrations of free fatty acids and serum concentrations of total bilirubin, apparent unbound bilirubin, and albumin were measured at regular intervals. Effects of the three regimens on serum bilirubin measurements were determined. The regimen of fat infusion and rate of infusion seemed to have no effect on serum concentrations of total and apparent unbound bilirubin, although there was a trend towards greater variability in apparent unbound concentrations with the intermittent regimen.

The use of fat emulsions for total parenteral nutrition of very low birthweight neonates has gained widespread acceptance in an attempt to provide better energy intakes The limited metabolic tolerance of tiny neonates, shown long ago with dextrose and amino acid solutions,[1] unfortunately applies also to lipids. Neonates with birth weights between 750 and 1500 g respond to infusion of fat emulsions with sharp increases in their plasma concentrations of total lipids, free glycerol, triglycerides, free fatty acids, and cholesterol.[2–4] These increases are quite unpredictable and variable in magnitude. As the greatest need for parenteral energy occurs during the first postnatal days when the liver has not yet reached its full bilirubin conjugating potential concern has been expressed about displacement of bilirubin from albumin in the presence of high concentrations of free fatty acids. This study was designed to compare the effects of three commonly used regimens for infusion of fat emulsions on serum bilirubin measurements.

Patients and methods

Tolerance to parenterally administered fat emulsions was studied in neonates weighing 1500 g or less at birth. Informed parental consent was obtained in all cases. Birth weights were recorded to the nearest 10 g. Gestational ages were determined from the mother's menstrual history, checked in most cases by sonographic determination of the biparietal diameter, and confirmed by physical examination of the neonate.[5] All neonates were normally grown—that is, their birth weights were between the 10th and 90th centiles for gestational maturity, sex, and race. Separate birthweight and gestational age curves were used for hispanic (Gibbs CE. Unpublished data.), white Anglo-American,[6] and black[6] babies. Neonates weighing less than 750 g at birth or with estimated gestational ages below 27 weeks were excluded from the study

The neonates were managed in accordance with the usual practices for our nursery. Phototherapy was used in all neonates from birth and generally continued throughout the study. Total parenteral nutrition was started on the third postnatal day unless otherwise indicated.[4] The neonates received fat emulsion (Intralipid, KabiVitrum, Alameda, California, United States) according to one of three randomly allocated regimens. Those in group 1 received the fat emulsion at a constant rate over 24 hours, beginning at a daily dosage of 1 g/kg and increasing by 1 g/kg on each successive day to a daily maximum of 4 g/kg. Those in group 2 received fat emulsion at a constant rate over 16 hours followed by eight hours without infusion of fats, daily dosage was the same as in group 1. Those in group 3 received fat emulsion at a constant rate over 24 hours with a daily dosage of 4 g/kg from the beginning of the infusion. Total parenteral nutrition fluids, fat emulsion excepted, were administered through an arterial umbilical catheter as long as the neonate required the catheter for blood gas monitoring. If the catheter was removed the fluids were administered through peripheral veins. The fat emulsion was infused through a peripheral vein used for no other purpose. No enteral feedings were provided during the study. Amounts of blood removed for study or clinical purposes were carefully tabulated and replaced by packed red blood cells whenever 7–10% of the baby's blood volume was estimated to have been removed. The study was stopped if a baby was unable to tolerate his or her regimen of fat emulsion—that is, if the plasma was frankly creamy on inspection whenever a blood sample was obtained for the study.

The study lasted eight days. Blood samples were obtained through the umbilical catheter (after clearing the line by removing 3 ml of blood, which were replaced after obtaining the blood sample) or by heelstick before beginning the fat emulsion and every 24 hours thereafter. Plasma concentrations of free fatty acids were determined in quadruplicate as previously described.[2] Serum concentrations of total bilirubin and apparent unbound bilirubin were determined in triplicate by a direct spectrophotometric technique.[7] Serum concentrations of albumin were determined in triplicate by a colorimetric technique.[8] Conjugated hyperbilirubinaemia did not occur in any neonate, with all direct bilirubin values being 17 µmol/l or less.

Statistical analysis. Each variable was analysed by means of one way analysis of variance to detect differences between the three groups at a given time during the study. When main effect differences were detected (F test, $p \leq 0·05$), Duncan's multiple range test was applied to locate differences between means for various groups. A significance level of $p \leq 0·05$ was chosen to define significance. Within each group, the mean value for each day of study was compared with the pre-infusion value by means of a one tailed Student's paired *t* test as mean values were predicted to increase or to remain stable but not to decrease. As eight comparisons within a set of data were made, $p \leq 0·10/8$ or $p \leq 0·013$ was needed to indicate significant differences. Relations between two variables were studied by regression analysis.

Results

Of the 39 neonates who were randomly allocated to one of the study groups, one baby in group 1 was consistently unable to tolerate fat emulsion: his plasma was frankly creamy when he was receiving only 1 g/kg/day of fat emulsion and he also poorly tolerated glucose and amino acids, his data were excluded from analysis. The remaining 38 neonates are described in the Table. Birth weights ranged from 820 to 1500 g, gestational ages from 27 to 34 weeks, and postnatal ages at the time of enrolment from 1 to 9 days. There were no significant differences between the three groups in mean birth weights, gestational ages, and postnatal ages.

Nine babies did not complete the eight day study. In group 1 one baby died of hyaline membrane disease. In group 2 two babies required surgical treatment for necrotising enterocolitis, one died of hyaline membrane disease, one had severe hyperlipaemia, one was removed from the study at the request of the parents, and in one the lipid infusion was interrupted inadvertently. In group 3 one baby had severe hyperlipaemia and one was removed from the study when enteral feedings were started inadvertently. Data from these babies up to the time of stopping the study were included in the analysis.

Plasma concentrations of free fatty acids ranged from 0·13 to 7·89 mmol/l. In groups 1 and 2 mean concentrations increased with the rate of lipid infusion and stabilised at a daily infusion rate of 4 g/kg. In group 3 concentrations increased sharply as soon as the lipid infusion started and remained fairly stable thereafter (Figure).

Mean serum concentrations of total bilirubin before infusion of lipids and during each day of lipid infusion are depicted in the Figure. In some in-

Table *Characteristics of the 38 neonates studied. Values are No or mean (SD) [range]*

	Group		
	1	*2*	*3*
No	14	13	11
Sex (M/F)	10/4	8/5	4/7
Race (H/W/B)*	12/1/1	8/3/2	8/3/0
Birth weight (g)	1190 (196) [820–1480]	1160 (218) [820–1500]	1160 (226) [820–1500]
Gestational age (weeks)	29 (1·7) [27–34]	29 (1·3) [27–31]	29 (1·3) [28–31]
Postnatal age (days)	4 (1·9) [1–9]	3 (1·6) [2–7]	3 (1·4) [2–5]

*H Hispanics, W Anglo-American, B Black

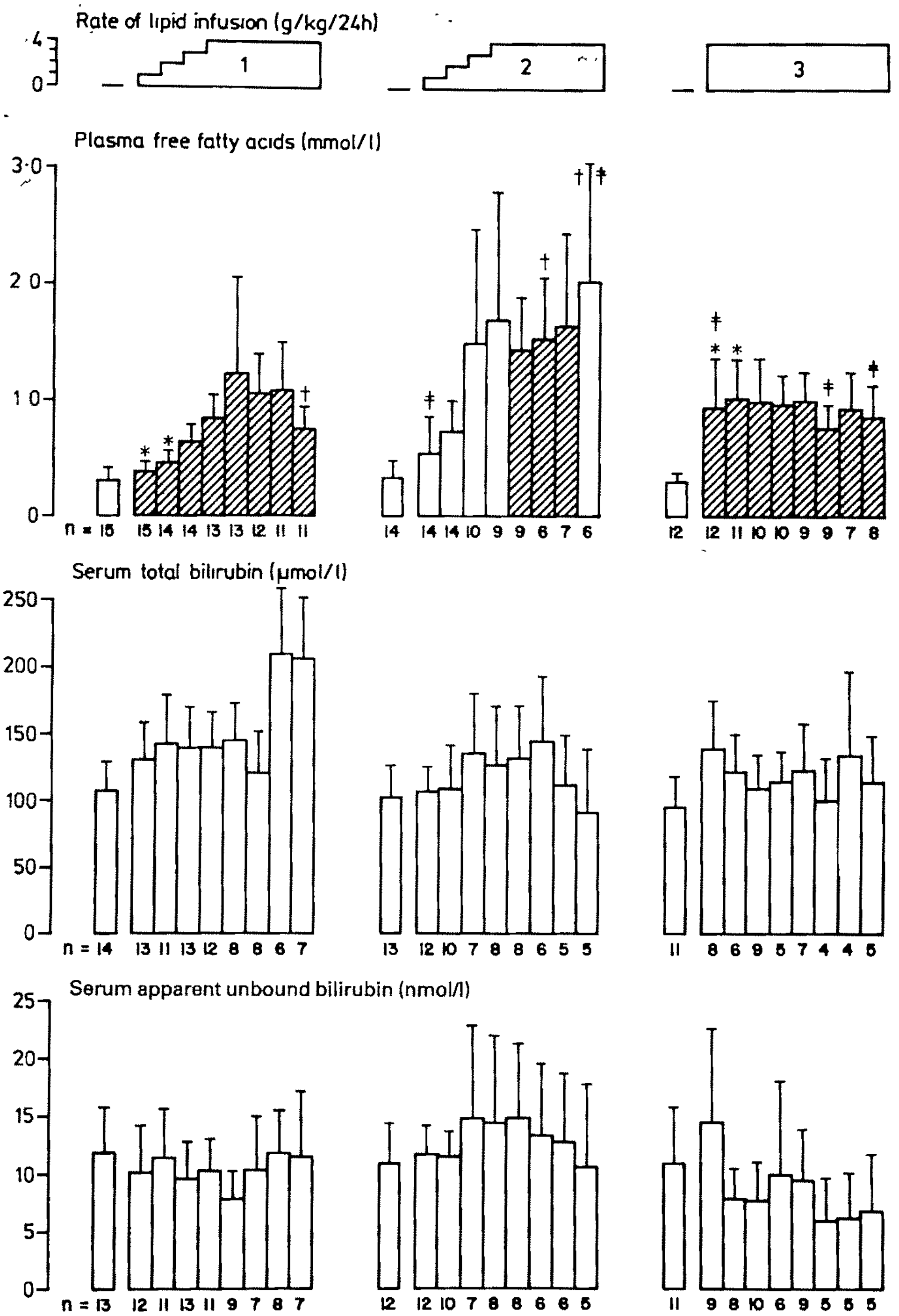

Figure *Mean (2SE) plasma concentrations of free fatty acids, serum concentrations of total bilirubin, and serum concentrations of apparent unbound bilirubin before and during infusion of lipids on each of the eight days of study. The corresponding rate of lipid infusion is shown at the top. Cross hatched bars denote mean values that are significantly greater than pre-infusion values for that group (*t *test, p≤0·013). Other symbols denote significant differences at a given time between groups 1 and 3 (*), groups 1 and 2 (†) and groups 2 and 3 (‡) (one way analysis of variance and Duncan's multiple range test, p≤0·05).*

stances concentrations were not measurable due to hyperlipaemia of the sample, characterised by a visible layer of cream after the blood sample had been centrifuged Within each group, bilirubin concentrations during infusion of lipids were not statistically different from pre-infusion concentrations—that is, the mean differences between concentrations on a given day or on a given rate of lipid intake and pre-infusion concentrations were not significantly different from zero. On a given day during the study mean bilirubin concentrations were similar for all three study groups. For individual neonates, bilirubin concentrations followed the trend that would be expected during the first one to two weeks after birth—that is, a rise followed by stable or decreasing values. No baby required any type of exchange transfusion during the study. Only five neonates in group 1, three in group 2, and three in group 3 had any measurable total bilirubin concentrations in excess of 171 μmol/l during the study.

Serum concentrations of apparent unbound bilirubin ranged from 1 to 45 nmol/l Only five neonates in group 1, three in group 2, and two in group 3 had any concentrations in excess of 20 nmol/l and only one in each group had concentrations higher than 30 nmol/l. There was no correlation between concentrations of apparent unbound bilirubin and concentrations of total lipids, free glycerol, triglycerides, and cholesterol Of particular importance was the absence of correlation between concentrations of apparent unbound bilirubin and free fatty acids. Within each study group, concentrations of apparent unbound bilirubin during infusion of lipids were not statistically different from pre-infusion concentrations. On a given day of study mean concentrations were similar for all three study groups (Figure)

Serum concentrations of albumin were not affected by either duration of lipid infusion or the regimen of lipid infusion. Mean (2 SE) pre-infusion concentrations were significantly lower in group 3 than in group 1 (392 (21·8) μmol/l *v* 441 (8·8) μmol/l, $p<0·05$). This small difference was most likely spurious as no continuous trend was evident and the difference, though significant, was of doubtful clinical importance.

Discussion

Theoretically, parenteral fat emulsions may affect the bilirubin metabolism of a neonate in two conflicting manners.

On the one hand, particles of fat emulsions are capable of binding unconjugated bilirubin in vitro.[9 10] This affinity for bilirubin is considerably weaker than the affinity of albumin, non-albumin serum proteins, and red blood cell membranes.[9] In vitro, fat particles may displace bilirubin from red cell membranes when the bilirubin:albumin molar ratio exceeds 2. Thus it is possible that fat particles exert some protective effect against bilirubin encephalopathy [10]

On the other hand, fat emulsions are metabolised in vivo, with resulting production of free fatty acids. Although the primary binding sites of bilirubin and free fatty acids on albumin are quite distinct, free fatty acids in high concentrations may encroach on the bilirubin binding site and displace bilirubin from albumin. Liberation of bilirubin may result in a rising concentration of unbound bilirubin, potentially increasing the risk of encephalopathy. Although it is usually recommended to keep the free fatty acid:albumin molar ratio below 6 to limit the risks of toxicity,[9] the ratios above which displacement of bilirubin might occur have been variably estimated at 4,[11 12] 5,[13] 6,[14] and 10.[9] In fact only one study has actually shown the occurrence of free bilirubin when the ratio exceeded 6.[14] Whether the circulating fat particles are able to bind the bilirubin that has been liberated by the excess of free fatty acids and to clear it through the reticuloendothelial system, thereby protecting the brain, remains speculative but is an interesting thought. There is in vitro evidence that a few of the medium chain fatty acids may improve the binding of bilirubin to albumin and that this effect varies with the length of the chain.[15] In our clinical study, however, the concentration of total free fatty acids seemed to have little effect on the concentration of apparent unbound bilirubin as measured by the peroxidase assay. Free fatty acids concentrations as high as 7·89 mmol/l were observed. Yet there was no correlation between apparent unbound bilirubin concentrations and concentrations of free fatty acids There are at least four possible explanations for these findings.

(1) Bilirubin may not be displaced from albumin, even at these high plasma concentrations of free fatty acids

(2) Bilirubin freed from albumin may be bound by other means—namely, non-albumin serum proteins, erythrocytic membranes, or lipid particles.

(3) Concentrations of apparent unbound bilirubin measured by the standard dilute assay may be falsely low, reflective of the 40-fold dilution in the system.

(4) Photoisomers of bilirubin IX alpha (ZZ) may differ in their interaction with free fatty acids

Interpretation of serum concentrations of apparent unbound bilirubin is hampered by the lack of pathological correlates.[16–18] Although, in theory at least, any amount of unbound bilirubin may jeopardise cerebral metabolism, it is not known how much unbound bilirubin must be present to produce bilirubin encephalopathy or whether there is a relation between the amount of unbound bilirubin and the severity of the cerebral insult. In this study we observed serum concentrations of apparent unbound bilirubin as high as 45 nmol/l without any detectable clinical signs of encephalopathy. Only one of the two babies who died during the study had a postmortem examination performed and he had no evidence of kernicterus; the maximal concentration of apparent unbound bilirubin in this baby was 16·4 nmol/l.

Previous studies have indicated that neonates who received intermittent infusions of fat emulsions showed evidence of considerable fluctuations in free fatty acid:albumin molar ratios and also had very high ratios (in excess of 15).[19] By comparison, this ratio did not fluctuate during continuous infusions of up to 2 g/kg per day. Over 2 g/kg, however, the ratios reportedly averaged 10 to 16.[19] This may be another argument in favour of continuous infusion of fat emulsions at a constant rate.

The observation that fat emulsions interfere with the spectrophotometric determination of serum bilirubin concentrations has been made previously.[20] In that study, however, the presence of fat particles caused an overestimation in the concentration of conjugated bilirubin, not of total bilirubin. In the present study creaminess of a plasma sample was not judged in the same way in the nursery where the samples were obtained and in the laboratory where they were assayed. If a plasma sample was judged in the nursery to be excessively creamy—admittedly, a very subjective judgment—the study was stopped and the baby excluded from the study. If, on the other hand, an occasional total bilirubin concentration was not measurable or spuriously raised in the laboratory because of their assessment of excessive creaminess, that particular value was not reported but the baby was not excluded from the study.

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Human milk vitamin content after pasteurisation, storage, or tube feeding

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SUMMARY We investigated the effect of the composition of the storage container, Holder pasteurisation, and conditions during tube feeding on the concentration of selected vitamins in human milk. Though the fat soluble vitamins A, D, and E were not affected, the concentration of several water soluble vitamins decreased. The lower vitamin C concentration of milk stored in polypropylene containers compared with milk stored in glass containers (29%) was not significant. Holder pasteurisation significantly lowered the concentrations of vitamins C (36%), folacin (31%), and B_6 (15%). Tube feeding significantly lowered the concentrations of vitamins C (44%) and B_6 (19%), and exposure to phototherapy seemed to lower the vitamin C concentration (53%) further.

Low birthweight infants have increased vitamin requirements. Vitamin losses in expressed human milk before or during feeding may increase the incidence of vitamin deficiencies in these babies.

The vitamin concentration of human milk may not satisfy the requirements of the preterm baby.[1] This problem could be aggravated if vitamin losses occur during pasteurisation and storage of the milk. Vitamin losses due to these factors have been extensively studied in cows' milk[2] but have received little attention in human milk.[1 3]

Further losses could occur during feeding due to exposure of the milk to light—for example, phototherapy—and by adsorption of vitamins to the walls of the containers and the tubing of the feeding system. These factors do influence the concentration of vitamins B_2 and B_6[4] and A, D, and E[5] of parenteral solutions. In human milk only the losses of vitamins B_2 and A during feeding have been studied.[6 7]

We therefore studied the influence of pasteurisation, composition of the storage container, and conditions during tube feeding on the concentration of selected vitamins in human milk.

Materials and methods

Milk samples. Milk was obtained from healthy mothers who were not receiving any medication or vitamin supplements. Their infants had been born at term and breast fed for one to eight months. Morning specimens were obtained using a hand suction pump (Kaneson^R^, Yanase Waitch, Osaka, Japan) and stored in polypropylene bottles (120 ml Axifeed^R^, Mecomfa, Lisse, The Netherlands), wrapped in aluminium foil in a domestic refrigerator (4°C) after standard instructions. All specimens were transported within four hours in iceboxes to the hospital, where they were immediately combined to make up nine different pools of 160 ml. After thorough mixing each pool was divided into five samples and the various treatments begun.

Control sample

Twenty ml from each pool were stored in two 10 ml sterile air tight containers, which were completely filled and covered in aluminium foil. The composition of these polypropylene containers was identical to that of the Axifeed bottle. All samples were stored at −20°C for three weeks until analysed. The fat soluble and B vitamin concentrations measured at this time were used as the control values for all experiments, while the vitamin C concentrations measured at this time were only used as the control value for the experiment on the influence of the composition of the storage container. As vitamin C is unstable[8] the control sample for the experiments on the influence of pasteurisation, feeding procedure, and phototherapy was handled differently: two ml from each pool were stored in a 2 ml sterile air tight container covered with aluminium foil, containing 2 mg reduced glutathione, at 4°C until vitamin C analysis within 48 hours after the milk collection

Effect of various treatments. All samples were stored in conditions identical to those of the control samples

Influence of the composition of the storage container

Twenty ml of each pool were stored in two 10 ml sterile air tight glass containers in exactly the same conditions as described for the control sample until vitamin analysis (which included analysis for vitamin C). This allowed us to compare the influence on the vitamin content of storage in the glass with the polypropylene container

Influence of pasteurisation

Holder pasteurisation, 62·5°C for 30 minutes, was performed on samples of 50 ml of each pool in sterile air tight polypropylene bottles (Axifeed) according to the recommendations of the Department of Health and Social Security.[9] Preliminary studies showed that our system warmed the milk samples to 62·5°C within eight minutes and subsequently cooled them to 20°C within five minutes. In this experiment two samples were discarded after a technical failure resulted in a prolonged heating period.

Losses during feeding

The feeding procedure used for low birthweight infants was imitated. A 20 ml sample of each pool was drawn up into a 20 ml sterile polypropylene syringe (Once, Asik, Denmark) and pumped at a rate of 4 ml/hour through 180 cm of polyvinylchloride (PVC) connecting tubing (Talas, Ommen, The Netherlands) and a 100 cm 5 charriere PVC feeding tube (Unoplast, Denmark) into a sterile polypropylene container protected from light by aluminium foil. The syringe, with an eccentric nozzle, was held at an angle of 30° to prevent accumulation of fat in the syringe [10] During the infusion time of five hours the system was exposed to the normal fluorescent lighting and temperature (28°C) of our neonatal unit.

Losses during feeding and phototherapy

Using the same infusion system as described above, the milk was also exposed to phototherapy for half an hour by running 100 cm of the connecting tubing through an incubator (32°C) placed under a phototherapy unit (four blue lamps Philips TL 20W/52 and four Sylvania daylight lamps F20 WID-RS, 35 cm above the tubing system)

Vitamin analysis. The following vitamins were measured by high performance liquid chromatographic methods. Vitamins A (all-transretinol)[11] and E (α-tocopherol)[12] were determined after alkaline saponification and vitamins B_2 and B_6 were analysed as their biologically active cofactors, flavin adenine dinucleotide[13] and pyridoxal 5′-phosphate,[14] respectively. Vitamin C was measured as L-ascorbic acid plus dehydro-L-ascorbic acid.[8]

The vitamin B_{12} content was measured by competitive protein binding assay using purified intrinsic factor (Sigma Chemical Company, St Louis, Missouri, United States).[15] Vitamin B_{12} was extracted in boiling 0·1M sodium acetate buffer (pH 4·8) containing 0·005% (weight/volume) potassium cyanide (15 minutes at 100°C). To reduce non-specific binding in the competitive protein binding assay, which is observed with milk samples using only acetate extraction, an alkaline denaturation step (20 minutes at 37°C in 0·1M sodium hydroxide) was performed before acetate extraction.

The folacin content was estimated as the 'free' 5-methyltetrahydrofolic acid (5-MeTHF) content by radioassay using purified folate binding protein (Sigma Chemical Company) as binder.[16] 5-MeTHF purified on reversed phase high performance liquid chromatography was used as the standard and tritiated pteroylmonoglutamic acid as the tracer. Milk folates were extracted in a boiling 0·2M borate buffer (pH 9·3) containing 1% (weight/volume) freshly added vitamin C. The presence of polyglutamate forms of 5-MeTHF may result in a slight overestimation of the free folacin content using a radioassay.[17]

Vitamin D was quantitated as the 25-hydroxyvitamin D (25-OHD) present in the lipid extract, which accounts for at least 75% of its antirachitic activity present in human milk. The 25-OHD content in the total lipid extract was quantitated by competitive protein binding assay,[18] but before the assay the extract was purified by straight phase high performance liquid chromatography.

Statistical analysis. Evaluation of the results was performed using the paired *t* test with the help of the department of statistics (Dr T Stijnen). To correct for multiple comparisons only p values <0·01 were regarded as significant.

Results

The composition of the storage container (Table 1)

Table 1 *Differences in vitamin concentrations of human milk stored in polypropylene or glass containers Values are mean (SD) [range]*

Vitamin	*n*	*Polypropylene*	*Glass*
A (μmol/l)	9	1·32 (0·83) [0·50–3·15]	1·39 (0·84) [0·54–3·25]
D (pmol/l)	8	143 (64) [68–260]	149 (59) [78–252]
E (μmol/l)	9	7·1 (2·8) [3·0–11·2]	7·7 (3·4) [3·3–15·0]
B_2 (μmol/l)	9	0·59 (0·16) [0·35–0·87]	0·57 (0·16) [0·34–0·81]
B_6 (nmol/l)	9	86 (36) [37–156]	90 (37) [39–161]
B_{12} (pmol/l)	8	309 (133) [157–523]	297 (128) [149–501]
Folacin (nmol/l)	8	73 (24) [42–110]	73 (25) [40–112]
C (μmol/l)	5	141 (45) [75–189]	174 (40) [127–209]

Table 2 *Influence of pasteurisation, tube feeding, and phototherapy on vitamins in human milk*

Vitamin	*Mean (SD) % remaining after*		
	Pasteurisation	*Tube feeding*	*Tube feeding + phototherapy*
A	103 (15)	94 (19)	102 (19)
D	103 (10)	101 (14)	100 (8)
E	106 (13)	100 (13)	100 (12)
B_2	94 (8)	98 (7)	97 (2)
B_6	85 (8)**	81 (12)**	83 (11)*
B_{12}	90 (10)	97 (6)	101 (7)
Folacin	69 (8)**	99 (12)	110 (17)
C	64 (12)**	56 (22)**	47 (22)**

*$p<0·01$,
**$p<0·001$

only affected the vitamin C concentration, which was 29% lower in the milk in the polypropylene containers compared with the milk in the glass containers. The fall in the vitamin C concentration was not significant ($p=0·02$)

Pasteurisation (Table 2) did not influence the concentrations of vitamins A, D, E, B_2, and B_{12} There were, however, significant losses of vitamins B_6 (15%), C (36%), and folacin (31%)

Delivery of the milk through a feeding system (Table 2) lowered the vitamin C and vitamin B_6 concentrations by 44% and 19%, respectively. Additional exposure of the milk in the tubing to phototherapy (Table 2) resulted in a similar fall in the vitamin B_6 concentration (17%) and a slightly greater fall in the vitamin C concentration (53%)

Discussion

Our study shows that the composition of the storage container, pasteurisation, and conditions during tube feeding can lower the vitamin content of human milk.

Plastic containers are preferred for storing fresh human milk because leucocytes are lost by adherence to the wall of glass containers [19] Plastic containers, however, may adsorb vitamins onto their walls In parenteral solutions vitamins A, D, and E are lost by adsorption to plastic.[5] We found that the concentrations of the vitamins A, D, E, B_2, B_6, B_{12}, and folacin were the same when the milk was stored by polypropylene containers compared with storage in glass containers. The lower vitamin C concentration in the polypropylene container was not regarded as significant in our study because of the multiple statistical comparisons performed These findings are, however, being followed up.

In addition to the influence that the composition of the containers has on the vitamin concentrations of human milk, the duration and the temperature of storage may influence the vitamin concentrations too. This is well known for vitamin C[7 20] and was taken into account in our study. Recently, however, Bank *et al* have shown that folacin concentrations may also fall in stored human milk,[20] although this was not found in a previous study.[21] Concentrations of other vitamins may also be unstable in human milk. We intended to study the vitamin content of our samples after three months' storage, but unfortunately lost all these samples due to refrigeration failure.

Holder pasteurisation is used by many milkbanks. Although its influence on the immunological components[22] and macronutrients has been studied, its influence, however, on vitamin concentrations has received little attention. We observed a significant decrease in vitamin B_6 concentrations, while vitamin A, D, E, B_2, and B_{12} concentrations remained stable, similar to the findings in cows' milk.[2] The observed decrease of vitamin B_6 may, however, have been the result of hydrolysis to its non-phosphorylated forms pyridoxal. The decrease of the vitamins C (36%) and folacin (31%) was greater than has been reported for cows' milk (20% and 10%, respectively).[2] Other methods of heat treatment using a shorter time[3] or a lower temperature[23] might be preferable. Goldblum *et al* found no decline of vitamin B_1, B_2, B_6, C, and folacin concentrations with rapid high temperature treatment.[3] Ford *et al* have already pointed out that

Holder pasteurisation of human milk decreases the bioavailability of certain vitamins—for example, folacin—by damaging their binding proteins.[22]

Vitamin losses from banked human milk may also occur during feeding because of photo-oxidation[6] or by adsorption to the tubing used.[7] We only found a significant loss of vitamins B_6 and C. Addition of phototherapy did not affect the vitamin losses except for a small increase in the loss of vitamin C. Previous studies with parenteral solutions showed a decrease in vitamins B_2 and B_6 due to photo-oxidation[4] and A, D, and E due to adsorption to the feeding system.[5]

In enteral feeding only vitamins A and B_2 had previously been studied: Bryant *et al* found no decrease of vitamin A in feeding formula[24] and Bates *et al* found a decrease of vitamin A and B_2 in drip human milk, which they suggested was due to photo-oxidation.[6] The discrepancies between these findings and ours need an explanation In the parenteral solutions studied no fat or proteins were present and in human milk binding of vitamins A, D, and E to these substances may limit adsorptive losses. The higher fat content of the expressed human milk used in our study may also have limited the penetration of light into the milk and prevented the vitamin A and B_2 losses due to photo-oxidation found by Bates *et al* in their study using drip milk,[6] which has a lower fat content. Furthermore, in the study of Bates *et al* the exposure time to phototherapy was much longer than in our study (six hours as against half an hour). Vitamins B_6 and C had not been studied previously in human milk, but studies in parenteral feeding[4] and cows' milk have shown that these vitamins are particularly sensitive to photo-oxidation. In our study we tried to imitate two feeding methods often used for low birthweight infants. Further studies are needed to investigate which of the factors present in these situations—for example, exposure time, intensity and wavelength of light, or environmental temperature—are the most important. It is also important to realise that photo-oxidative losses during collection of milk by the mother or preparation of feeds in the neonatal unit could also occur.

In conclusion, we found a significant decrease of several vitamins in human milk during storage (vitamin C), pasteurisation (vitamins B_6, folacin, and C), and delivery through a tubing system (vitamins B_6 and C). These losses could accumulate as in routine use the milk passes through all these stages.

The low birthweight infant is born with marginal reserves of fat soluble vitamins and may require more water soluble vitamins.[1] It seems that routinely used methods for processing and feeding human milk to low birthweight babies do not influence the concentration of fat soluble vitamins but do lower the concentration of water soluble vitamins. Supplementation with water soluble vitamins may be necessary when the low birthweight infant is fed with expressed human milk.

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Knemometry in assessment of linear growth

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SUMMARY A rigorously designed auxological study was carried out to assess the operational characteristics of the knemometer and the value of short term lower leg and height measurements in estimating and predicting rates of linear growth. Measurements were made on 18 normal children monthly for six months and on six normal children weekly for six weeks. Six other children measured weekly underwent tonsillectomy after three weeks to determine the effect of stress on growth. The measurement protocol permitted estimations of both inter- and intraobserver variation.

Knemometry is a sensitive, precise, and robust technique that enables accurate measurements to be made of the lower leg by interchangeable observers. The lower leg does not grow smoothly and variations in growth rate seen in both healthy children and children with transient intercurrent stress limit the practical clinical value of knemometry to the measurement of linear growth in the short term.

The knemometer (Fig. 1) is an instrument designed to measure the length of the lower leg with great accuracy,[1] thereby permitting the calculation of rates of linear growth at time intervals as short as daily[2] or intradaily.[3] The availability of this technique has led to speculation that it may be useful in measuring the growth response to different forms of treatment in shorter time intervals than has been possible hitherto. The only published assessment of the operational characteristics of the knemometer is that of the inventors,[1] and no study has been reported describing the relation of lower leg growth to that of overall height or of the value of short term measurements to predict growth in the longer term The machine is expensive and the technique specialised and fairly time consuming. We have therefore performed an audit of knemometry to assess its strengths and weaknesses as a clinical research tool.

Methods

The measurers were an auxologist (M), two research nurses (C and S) and a paediatrician (J), all of whom had been instructed in the use of the knemometer by its inventor, Dr I M Valk. All measurements were made between April and September 1985 in the action laboratory at our hospital Every time a child attended the laboratory single measurements were made in the following sequence: weight (Avery beam balance), standing and sitting height[4] (Harpenden Stadiometers), and mid-triceps and subscapular skinfold thickness (Holtain calipers). Then followed measurements of lower leg length by knemometry.

The child was placed on the adjustable seat with the position of the feet on the measurement table determined by an individually drawn template used at each visit. When the child was comfortable and relaxed a horizontal measuring plate connected to an electronic Sony Digiruler (Sony Magnescale Inc, Japan; measurement interval 0·1 mm) was placed on the upper surface of the knee. The child was then moved backwards and forwards on the frictionless chair mount and the leg moved from side to side until a stable maximum reading was achieved. Six sequential determinations of tibial length were made at each visit in the monthly study and four at each visit in the weekly study, the child leaving the seat and walking a few steps between each measurement.

At each attendance the child was measured by two observers working sequentially and totally independently The same observer pair then measured the child at each subsequent visit. At the first visit each observer positioned the child on the knemometer and noted the settings, which were then used by that observer in all subsequent visits to allow reproducible placing of the child. On 27 occasions the designated observer was absent and a substitute observer used the designated observer's settings to position the child. All readings of

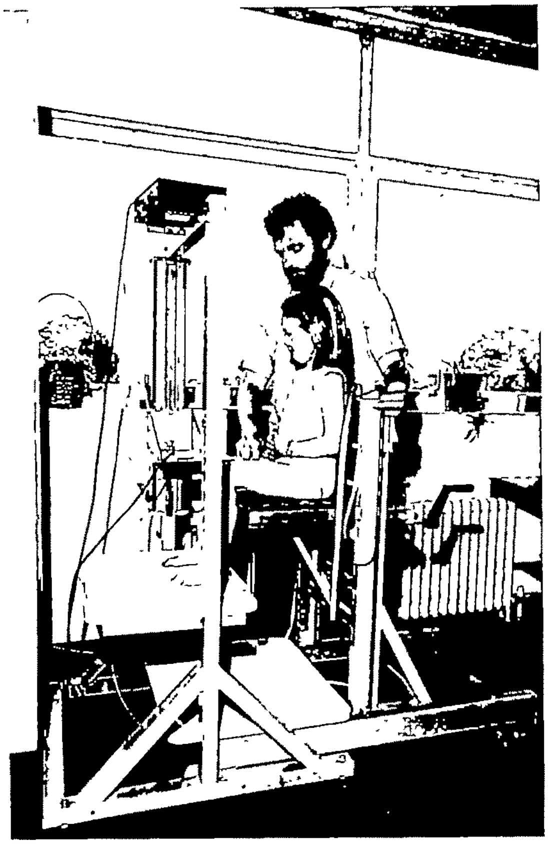

Fig 1 *The knemometer in use*

conventional auxology and knemometry were recorded on counterfoil and stored immediately in sealed envelopes until analysis at the end of the study. At each visit notes were made on the child's activities and any symptoms or illness that had occurred since the last visit All measurements on a child were made on the same weekday between 1500 and 1800h to coincide with the described intradaily plateau of postural change in lower leg length.[3] No child defaulted a planned measuring visit. Informed parental consent was obtained in all cases and the study was approved by the hospital ethical committee.

Subjects

All the children were white local residents from the middle and professional classes.

Monthly measurements. Six normal boys (aged 5·5 to 9·8 years) and 12 normal girls (aged 5·5 to 10·5 years) were measured for six months.

Weekly measurements. Six children (three boys and three girls aged 7·0 to 10·0 years) were measured for six weeks and once more 12 weeks later They were all in good health at the start of the study but by chance all three boys had mild, self limiting illnesses during the study, whereas the girls remained well Six further children (four girls and two boys aged 3·7 to 13·4 years) were measured weekly for three weeks before and after tonsillectomy

Results

Variation in measurement within and between observers. The sets of six knemometry readings made at monthly intervals by the four observers were analysed. The number of sets for each observer was: M 83, J 60, C 56, and S 53. The mean coefficients of variation for a set of six readings were 0·09, 0·08, 0·10, and 0 10%, respectively. The maximum coefficient of variation observed was 0·25%. The coefficient of variation for an observer did not change with increasing experience, indicating that a learning phenomenon did not occur during the six month study. The reproducibility of knemometry measurements experienced in the monthly study led to the decision to reduce the number of readings to four in a set in the study of normal children measured weekly There were 72 sets of four readings made by the four observers in which the maximum coefficient of variation was 0·13%

Measuring the children by pairs of observers made it possible to analyse if there was a systematic variation in estimates of lower leg length between members of a pair. In 126 pairs of measurements there were eight in which both observers obtained the same result. If the null hypothesis is that observer 'a' measures greater than observer 'b' randomly then a>b on 59 occasions and vice versa. In fact a>b occurred on 109 occasions, indicating a highly significant ($p<0\cdot001$) systematic variation. Inspection of the two most common measuring pairs showed that the variation was specific for each child but not for each observer (Table 1), leading to the conclusion that the difference between observers in the estimate of lower leg length was a function of the initial, and therefore subsequent, positioning of the child on the knemometer by that observer This interpretation was reinforced by the observation that on the 27 occasions when an observer substituted for an absent colleague the measurement of lower leg length was in harmony with the previous and subsequent measurements made by the original observer.

In contrast to the systematic variation in measurement of lower leg length, there was no significant

Table 1 *Maximum difference (cm) between the two principal pairs of observers for measurements of height, sitting height, and lower leg length in individual children*

Pair of observers	*Measurement*		
	Height	*Sitting height*	*Lower leg*
M and C	1·4 (1)	1·6 (2)	0·12 (6)
	0·5 (0)	1·4 (3)	0·11 (7)
	0·4 (0)	1·1 (4)	0·12 (5)
	1·1 (3)	1·0 (2)	0·24 (4)
	1·0 (1)	1·4 (2)	0·09 (7)
	0·3 (0)	1·3 (3)	0·12 (3)
	0·5 (2)	0·5 (4)	0·07 (4)
Mean (SD)	0·7 (0·4)	1·2 (0·4)	0·12 (0·05)
J and S	1·7 (2)	1·6 (0)	0·07 (7)
	1·2 (0)	0·7 (1)	0·11 (0)
	1·4 (1)	2·6 (2)	0·04 (0)
	0·6 (0)	1·4 (0)	0·28 (1)
	1·4 (2)	3·6 (3)	0·28 (5)
Mean (SD)	1·3 (4·0)	2·0 (1·0)	0·16 (0·12)

The figures in parentheses (except for the standard deviation values) show the number of times out of seven when the first observer measured higher than the second observer

difference between observers in the estimates of increment in lower leg length at monthly intervals. The pair of observers made identical determinations of lower leg length increment in five of 108 estimations and in the remainder observer 'a' estimated a greater increment than observer 'b' in 49 of 103 estimations, which did not differ significantly from that expected by chance, which was 51 of 103. These results led to the conclusion that knemometry is a precise technique for measuring increments in lower leg length at monthly intervals and that trained observers can substitute for each other so long as the child is positioned consistently for each measurement.

Height and sitting height were measured once only at each visit so no estimate of intraobserver variation could be made. When the measurements of height and sitting height were analysed by the two principal pairs of observers (Tables 1 and 2) there was a consistent difference for height between observers M and C and observers J and S that was observer specific but not child specific. The maximum difference between two observers in seven measurements on one child was 1·6 cm for height and 2 cm for sitting height, which illustrates the greater difficulty in measuring sitting height. Analysis of measurements of height and sitting height by the five observer pairs showed significant systematic differences in six out of 10 pairings (Table 2). These results confirmed that measurement of height and sitting height are more prone to systematic observer variation than is knemometry.

Table 2 *Mean (SEM) difference (cm) in measurements of height and sitting height by different pairs of observers*

Pair of observers	*No*	*Height*		*Sitting height*	
		Mean	*(SEM)*	*Mean*	*(SEM)*
M and S	14	+0·32 (−0·7)	(0·07)**	−0·37 (+0·9)	(0·14)*
M and C	49	−0·35 (−1·3)	(0·05)**	−0·03 (±0·9)	(0·004)
M and J	14	+0·23 (−1·1)	(0·12)	+0·47 (+1·1)	(0·14)*
J and S	35	−0·62 (−1·5)	(0·08)**	−0·47 (−2·0)	(0·15)*
J and C	14	−0·15 (+1·6)	(0·14)	+0·02 (+1·6)	(0·19)

Results show the measurement made by the first observer minus that made by the second observer. Largest difference between observers is shown in parentheses

*$p<0{\cdot}05$, **$p<0{\cdot}001$

Calculation of linear growth velocities. The seven measurements of lower leg length, height, and sitting height made on the 18 normal children by each observer were used to calculate rates of growth by linear regression of each measurement on decimal age (Table 3). The same calculation permitted an estimate to be made of the mean goodness of fit of the three derived velocities by each observer (Table 4), from which it can be seen that the professional auxologist (M) was the best measurer of height and sitting height but that there was no significant difference between the four observers' skill in knemometry. The overall goodness of fit for lower leg length was some four times better than that for height or sitting height, reflecting the precision of knemometry.

The relation between lower leg and height measurement was examined by correlating the derived height (H) and lower leg (LL) velocities. The resulting equations for the four observers were:

M: $H=2{\cdot}75\,LL-0{\cdot}1$ ($n=11$, $r=0{\cdot}76$);
J : $H=1{\cdot}49\,LL-10{\cdot}8$ ($n=9$, $r=0{\cdot}32$);
C: $H=1{\cdot}43\,LL+2{\cdot}7$ ($n=9$, $r=0{\cdot}62$);
S : $H=1{\cdot}84\,LL+2{\cdot}3$ ($n=7$, $r=0{\cdot}52$).

These show that measurement of lower leg length was an indifferent and unpredictable estimator of growth in height. Not surprisingly, lower leg length was an even poorer predictor of growth in sitting height (results not shown).

From the results presented in Table 3 it was possible to calculate the percentage variation between the two principal pairs of observers M and C and J and S in their estimates of height or lower leg velocity. For example, for case 11 the estimate of height velocity by J was 5·1 cm/year and by S 6·6 cm/year. The difference between J and S (1·5 cm/year) expressed as a percentage of the mean velocity (5·85 cm/year) was 26%. The mean (SEM) difference in height velocity for all five subjects made by J and S was 16 (3)% and for lower leg

Table 3 *Velocity (cm/year) for height, sitting height, and lower leg calculated for each case and each observer*

Case No	Observer											
	M			J			C			S		
	Height	Sitting height	Lower leg	Height	Sitting height	Lower leg	Height	Sitting height	Lower leg	Height	Sitting height	Lower leg
1				7 5	3 0	2 57	6 5	1 5	2 66			
2				8 9	5 7	2 13	5 8	2 6	2 65			
3	7 0	5 8	2 00							6 1	8 8	2 16
4	5 2	2 1	1 81				6 0	1 5	1 54			
5	4 6	2 0	1 84							5 1	3 3	1 84
6	5 7	2 5	2 03				5 5	4 2	1 90			
7	5 3	2 0	2 29				5 2	1 5	2 27			
8	6 5	1 0	2 01	8 5	4 5	1 96						
9	5 5	2 2	2 20	7 8	4 6	2 09						
10	5 4	2 2	2 30				5 4	2 4	2 49			
11				5 1	3 0	2 34				6 6	6 8	2 35
12	6 0	3 6	2 00				5 3	3 3	2 05			
13	9 1	5 9	3 04				8 7	4 4	3 08			
14				8 0	3 6	2 08				7 2	4 3	1 90
15				7 2	4 3	1 91				6 2	4 6	1 99
16				8 5	5 6	2 57				7 8	5 9	2 96
17				5 9	2 6	2 53				7 2	8 1	1 99
18	5 4	1 5	2 01				5 8	0 1	1 99			

Velocities were calculated from the linear regression of seven monthly measurements on decimal age

Table 4 *Mean (SD) goodness of fit of derived velocities (cm/year) of height, sitting height, and lower leg length, analysed by observer*

Velocity	*Observer*			
	M	*J*	*C*	*S*
Height	0 18 (0 06)	0 33 (0 08)	0 29 (0 11)	0 39 (0 13)
Sitting height	0 18 (0 06)	0 47 (0 19)	0 61 (0 36)	0 48 (0 26)
Lower leg	0 06 (0 01)	0 07 (0 01)	0 06 (0 01)	0 08 (0 05)

Goodness of fit was calculated as the square root of the residual mean square of the seven observations used to calculate the velocity

velocity was 12 (4)%. For M and C the results on seven subjects were 5 (1)% for height velocity and 5 (2)% for lower leg length velocity These results show the difference between the 'two pairs of measurers but more importantly also show that lower leg length velocity calculations were not more reproducible within a pair of observers than were height velocity calculations.

The power of measurements of lower leg length or total height over periods of less than six months to predict the overall six monthly growth velocity calculated from all seven observations is analysed in Table 5. Observations made by the best measurer on 11 normal children were used The results show that there is little difference between the reproducibility of lower leg and height velocities and that measurements of either made monthly over five months will predict the six monthly velocity within 15% in roughly 97% of cases. Over four months the prediction widens to 18·6% (mean (2 SD)) for lower leg velocity and 28·8% for height velocity Shorter time intervals produced even poorer predictions

The weekly growth of normal children. Measurements of lower leg length every week in the six normal children are shown in Figure 2. The parallelism of the records made by each pair of observers is

Table 5 *Predictive value of lower leg and height velocities based on observations made at monthly intervals*

Measurement period (months)	*No of measurements*	*Mean (SD) deviation from reference velocity (%)*	
		Lower leg	*Height*
5	6	6 4 (4 5)	5 5 (3 8)
4	5	8 8 (4 9)	11 4 (8 7)
3	4	15 6 (11 3)	18 3 (14 4)
2	3	28 7 (23 7)	21 8 (11·3)
1	2	50 8 (46 2)	52 2 (34 6)

The figures are obtained from the 11 children measured by the most accurate observer (M) The reference velocity is that calculated from seven monthly observations, and the percentage deviation is defined as the difference between the reference velocity and the observed velocity

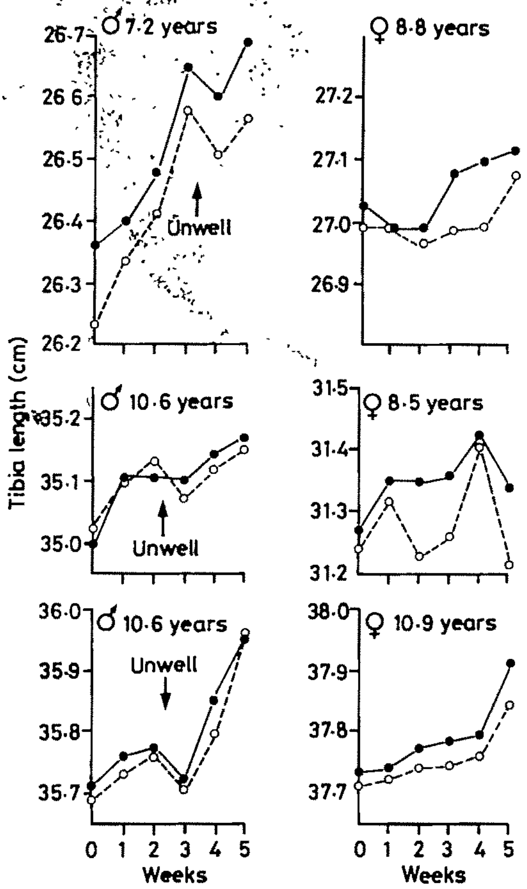

Fig. 2 *Graphs showing lower leg length of six normal children measured by knemometry weekly by two independent observers. The three boys (shown on the left) had mild self limiting illnesses indicated by the arrow The three girls (shown on the right) were asymptomatic*

evident as well as the uneven nature of lower leg growth. Each of the three boys suffered a mild self limiting illness during the study, and this coincided with a decrease in lower leg length. Despite the three girls being asymptomatic, they too had uneven lower leg growth

Each of the six children returned for a final measurement of lower leg length and height three months later. This permitted a comparison to be made between the estimate of growth velocity from seven measurements at weekly intervals with an estimate made from two measurements 12 weeks apart (at six and 18 weeks). When the predicted lower leg velocity (measured from weeks 0 to 6) was expressed as a ratio of the subsequent actual velocity (weeks 6 to 18) the values were: 0·57, 0·90, 1·45, 1·64, 1·76, and 3·2, with a mean of 1·58. When predicted height velocity was expressed in this way the values were: 0·37, 0·38, 0·52, 0·55, 0·57, and 0·93, with a mean of 0·56. Averaging the results from a pair of observers did not improve matters. These findings show that seven weekly measurements of lower leg length overestimate, whereas measurements of height underestimate, growth in the next three months.

The weekly growth of children before and after tonsillectomy. Six children measured weekly for three weeks before tonsillectomy had a mean (SD) increase in lower leg length of 0·12 (0·03) cm. In the

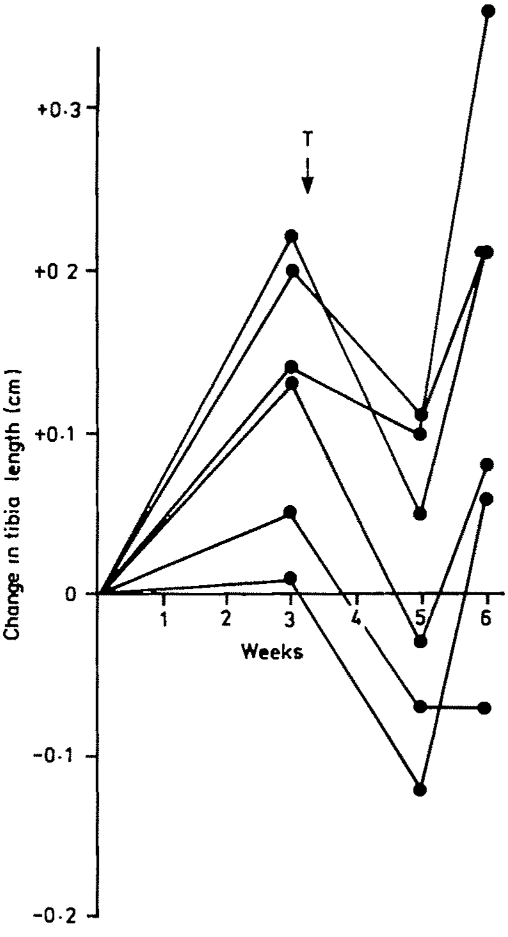

Fig. 3 *Change in lower leg length in six children measured by knemometry weekly for three weeks before tonsillectomy (indicated by T and arrow) and for three weeks thereafter The lines joining the points at 0, 3, 5, and 6 weeks are the best fit*

two weeks immediately after the operation there was a significant decrease in lower leg length of −0·11 (0·04) cm and in the sixth week of study there was catch up growth of +0·14 (0·06) cm. These observations are shown graphically in Figure 3.

Discussion

The study was designed to answer three questions. Firstly, how good is the knemometer at measuring lower leg length? Secondly, how does the lower leg grow and what is its relation to growth in absolute height? And thirdly, can measurement of lower leg length in the short term be used to predict future growth and hence shorten the time needed to assess the efficacy of growth promoting treatment.

Earlier work reported that knemometry can document changes in lower leg length weekly, day by day, or even within a day.[1-3] (Valk IM Personal communication.) We have confirmed some of these claims and have shown the device to be a precise, robust, and sensitive means of measuring changes in lower leg length. After a brief period of instruction observers quickly became proficient in the technique We have shown that observers may interchange so long as care is taken in positioning the child in exactly the same manner from visit to visit; this adds practical flexibility to clinical measurement. The consistently low coefficient of variation between readings taken at a single visit by one observer meant that four observations were adequate for the determination of lower leg length. In this study the arithmetic mean of six or four observations was always used, but in future work we would recommend that four observations should be made and if one was deviant it should be discarded. A modal estimate of lower leg length will be as good as or better than the arithmetic mean The answer to the first question is unequivocally favourable: the knemometer is an excellent tool for measuring lower leg length.

The precision of knemometry revealed an irregular pattern of lower leg growth from week to week, which was explicable in some cases, such as the children who suffered short illnesses or underwent tonsillectomy, but not in others. This meant that the precision of the technique in detecting small changes in lower leg length became a potential liability if the observer wished to use the measurements as an indicator of linear bodily growth overall. Different parts of the skeleton grow at different rates before and during puberty[5] and it was therefore not surprising that there was an indifferent correlation between growth of the lower leg and total height over six months. More noteworthy was the observation that there was little difference between height and lower leg increments in the value of measurements made over shorter time intervals than six months in the estimation of a six month velocity. The loss of predictive value in height measurements is inherent in the technique, whereas the loss of predictive value in lower leg measurements is due to the inherent irregularity of growth of the lower leg. Thus for the measurement of growth over six months or longer height is preferable to lower leg length because the technique is simpler, the apparatus less costly, and the clinician is interested in the overall stature of the patient.

Knemometry may have a place in the evaluation of short term changes in growth rate and thus be useful in assessing response to treatment. If used for this purpose it is important to have multiple observations—for example, five weekly readings over one month—to derive a lower leg length velocity before treatment and then a similar period of measurement on treatment. Used in this way knemometry could be used to screen patients, those responding to treatment in the short term then meriting a longer therapeutic trial monitored by conventional auxology.

We are grateful to the children and their parents who volunteered for this study, to Mrs S Amos, Mrs M Pickering, and Mrs C Grieve who made most of the measurements, and to Sanofi UK who provided the knemometer and financial support Statistical advice from Dr I R Dunsmore of the department of probability and statistics, University of Sheffield, is acknowledged Also our thanks to Mr P D Bull, Consultant ENT Surgeon, for allowing us to measure his patients

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Oral methotrexate is as effective as intramuscular in maintenance therapy of acute lymphoblastic leukaemia

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SUMMARY It has been postulated that variations in methotrexate absorption may influence the outcome of treatment in lymphoblastic leukaemia. One hundred and forty four children with acute lymphoblastic leukaemia not of the T cell type were randomised to receive continuing treatment with daily 6-mercaptopurine, vincristine, and prednisolone six weekly and methotrexate once weekly, either as a single oral dose or an intramuscular injection. Analysis of results with a minimum follow up of three and a half years has shown that the route of administration of methotrexate has had no influence on relapse at any site, but more children receiving intramuscular methotrexate died in remission. These results indicate that oral methotrexate is as effective as intramuscular methotrexate in continuing treatment of lymphoblastic leukaemia.

Methotrexate is one of the two most widely used drugs in continuing (maintenance) treatment of acute lymphoblastic leukaemia. The drug is usually given by mouth but its absorption is variable[1] [2] and influenced by factors such as timing and content of meals.[3] Parenteral administration of the drug circumvents the problem of variable absorption and thus might theoretically decrease the rate of bone marrow and testicular relapse in children with leukaemia by achieving more reliable blood concentrations. We report here the results of a clinical trial in which children with lymphoblastic leukaemia were randomly assigned to receive methotrexate weekly during continuing treatment, either by mouth or by intramuscular injection.

Patients and methods

All patients with acute lymphoblastic leukaemia not of T cell type, attending the Hospital for Sick Children between June 1979 and December 1982 were treated with the protocol as illustrated in Figure 1. Induction therapy consisted of oral prednisolone, subcutaneous L-asparaginase, and intravenous vincristine (Oncovin) and daunorubicin. Central nervous system (CNS) prophylaxis comprised intrathecal methotrexate on days 22 and 35 and four more doses at weekly intervals during and just after cranial irradiation. The dose was adjusted for age as follows: up to 6 months, 3 mg; up to 1 year, 4 mg; up to 2 years, 5 mg; up to 4 years, 7·5 mg; and over 4 years, 10 mg. Cranial irradiation was given at a dose of 24 Gy in 15 fractions over three weeks until January 1981, when after the report from the children's cancer study group[4] the dose was reduced to 18 Gy in 10 fractions over two weeks. Radiotherapy was deferred in children under 2 years at the time of diagnosis; they received intrathecal methotrexate on three consecutive weeks after induction and then every six weeks until radiation, which was given soon after their second birthday.

After CNS prophylaxis patients received continuing treatment with methotrexate at a single weekly dose of 20 mg/m^2 given either first thing in the morning by mouth, before breakfast, or as a single intramuscular injection, 6-mercaptopurine for two weeks in three at an optimum dose of 75-100 mg/m^2, adjusted if necessary to maintain the neutrophil count above $1{\cdot}0\times10^9$/l at the start of each two week course, and vincristine and prednisolone every six weeks. Patients were randomly assigned to receive their methotrexate either by mouth or as a single intramuscular injection. The protocol was designed so that patients received the standard dose of methotrexate throughout, with only 6-mercaptopurine being adjusted to the maximum tolerated dose. Prophylactic co-trimoxazole was

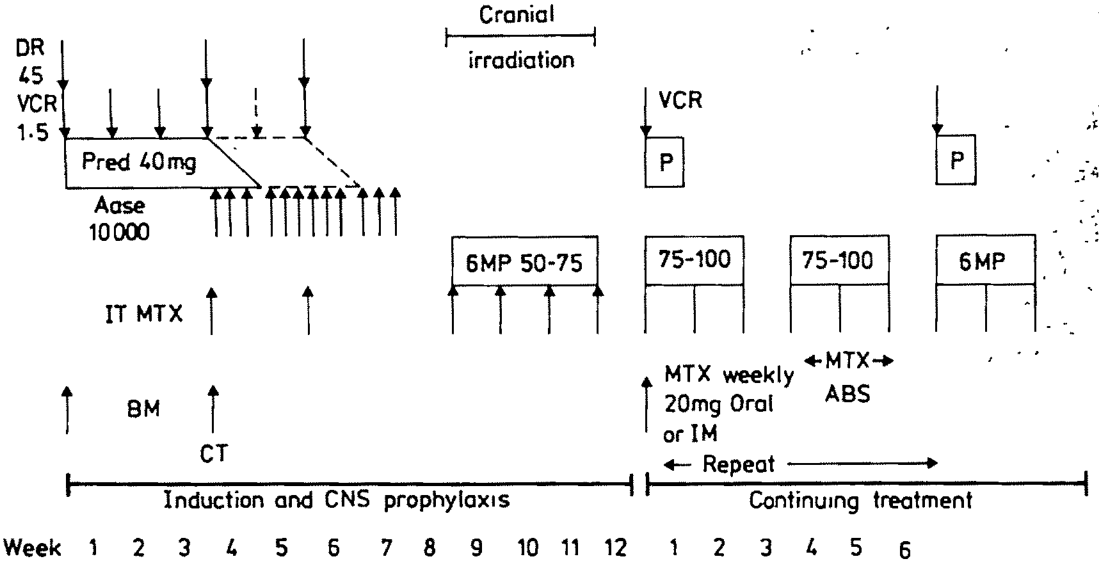

Fig. 1 *Design of the protocol Numbers refer to doses of drug in mg/m²/surface area except for L-asparaginase, which is in units/m²/surface area.*

Pred, P=prednisolone, VCR=vincristine, Aase=L-asparaginase, DR=daunorubicin, 6MP=6-mercaptopurine, MTX=methotrexate, IT=intrathecal, IM=intramuscular, BM=bone marrow, CT=computed tomogram, CNS=central nervous system, ABS=absorption

given only to patients who had had an episode of *Pneumocystis carinii* pneumonitis. This treatment was continued for 96 weeks of maintenance. Bone marrow examination, lumbar puncture, and, in boys, testicular biopsy examination were performed before stopping treatment.

Consent for randomisation was obtained verbally from the parents of all patients who were certain to be available for complete follow up. All other patients received oral methotrexate. Permission for the study was given by the joint committee on ethical practice of the hospital and institute.

All patients have been followed up for a minimum of three and a half years—that is, for at least 18 months after stopping chemotherapy—and median follow up of survivors who are free of disease is 62 months. Statistical analyses were performed by the log rank method.[5]

Results

Induction and randomisation. One hundred and sixty four patients were entered into the study, of whom 158 (96%) achieved remission, 154 at 21 days and the other four by 35 days. Two patients died during induction, one with renal failure and pulmonary haemorrhage and one, a boy with a history of bone marrow aplasia and jaundice, with septicaemia. Four patients were not in remission by 35 days, one boy with Ph' positive acute lymphoblastic leukaemia, one infant with leukaemia in association with a 4:11 translocation, and two boys with common acute lymphoblastic leukaemia and no obvious adverse prognostic factors

One hundred and forty four of the patients were randomised to receive oral or intramuscular methotrexate. Table 1 gives details of the patients

Table 1 *Details of patients who were randomised**

Administration of methotrexate	*(n=)*	*Sex (M F)*	*Age (years)*			*Presenting leucocyte count (x 10^9/l)*		
			<2	*2–10*	*>10*	*<20*	*20–50*	*>50*
Oral	(75)	40 35	12	58	5	55	8	12
Intramuscular	(69)	34 35	6	57	6	49	15	5

*Fourteen patients were not randomised seven with uncertain follow up studies, four who declined, two with radiotherapy violations, and one with CNS disease at presentation

Table 2 *First events in patients randomised*

Administration of methotrexate	*At risk*		*Any event*			*Death in remission*	*Relapse*									
							*Bone marrow**			*Central nervous system**			*Testis†*			*Other‡*
	All	*Boys*	*O*	*E*	*p Value*		*O*	*E*	*p Value*	*O*	*E*	*p Value*	*O*	*E*	*p Value*	
Oral	75	40	27	30·18	0·19	1	18	18·12	0·48	6	5·8	0·48	5	6·07	0·26	1
Intramuscular	69	34	30	26·82		3	16	15·8		7	5·2		6	4·93		2

*Two combined central nervous system and marrow relapses in each group
†Two combined marrow and testicular relapses on both oral and intramuscular methotrexate
‡One relapse in each in ovary, eye, and lymph nodes

who were randomised and also the reasons that 14 patients were not randomised Of the two radiotherapy violations, one child developed arachnoiditis and was therefore given craniospinal irradiation rather than further intrathecal chemotherapy, and the second child developed an intracranial haemorrhage during induction and was therefore not given cranial irradiation.

Outcome in the patients who were randomised. The outcome in the two groups of patients is shown in Table 2 and Figure 2. There was no difference in the incidence of relapse at any site between patients receiving oral and intramuscular methotrexate, and disease free survival was similar in the two groups of patients. Actuarial disease free survival at 6 years, with 95% confidence limits, was 63·9 (±11)% for patients who received oral methotrexate and 51·2 (±15·8)% for those who received the drug intramuscularly. There were no differences revealed in relapse rate between the two groups either when patients were stratified by age, leucocyte count, or immunological subclass of leukaemia or when classified as average or poor risk on the basis of age and leucocyte count (Table 3).

The alteration in the dose of cranial irradiation was not made in a randomised way, but there is no significant difference yet in the CNS relapse rate between the two radiotherapy schedules, CNS

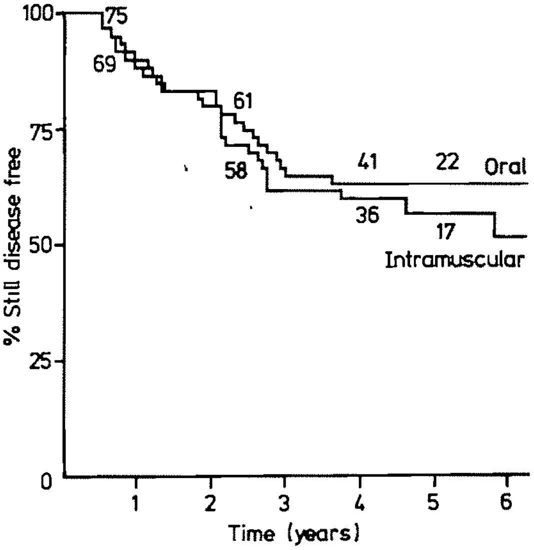

Fig. 2 *Disease free survival from randomisation in children receiving oral and intramuscular methotrexate The numbers on the graphs refer to numbers of patients at risk at the start of each 12 month period*

Table 3 *First event according to risk group*

	Administration of methotrexate				*p Value (oral v intramuscular)*
	Oral		*Intramuscular*		
	Events	*No at risk*	*Events*	*No at risk*	
Average	13	45	15	41	0 3
Poor	14	30	15	28	0 3

Average=Aged 2–10, initial leucocyte count $<20\times10^9$/l
Poor=All other patients

relapse occurring in six of 65 patients diagnosed before and seven of 79 diagnosed after 1981.

Toxicity. Induction therapy was well tolerated, with a mean time in hospital of eight days; 49 (30%) patients became febrile during induction and required a course of intravenous antibiotics for a presumed infection, which was serious in eight (5%). The infection rate during continuing treatment is shown in Table 4, where details are also given of the patients who were not randomised. Sixty children (38%) had at least one admission to hospital for presumed infection during treatment. The death rate during remission was 4%, half the deaths being due to measles. Two of the remission deaths occurred in children who had not been randomised, both with Down's syndrome and both probably due to mycoplasma pneumonia.

The major morbidity was due to fits, which occurred during or after treatment in two children randomised to oral and five randomised to intramuscular methotrexate Computed tomogram changes suggestive of methotrexate radiation toxicity were seen in one child who suffered fits on oral methotrexate and in three of the five on intramuscular methotrexate.

Factors affecting duration of remission. As there was no significant difference in outcome between the two groups of patients, prognostic factors were assessed for all 164 children entering the protocol. The factors influencing prognosis are shown in Table 5, the most important being leucocyte count, age, and morphological subclass of acute lymphoblastic leukaemia.

Table 4 *Infections during continuing treatment*

	Administration of methotrexate		
	Oral	*Intra-muscular*	*All patients*
Children admitted once or more during maintenance	29/75	28/69	60/158
Pneumocystis carinii	2 (1)	3	6 (1)
Varicella zoster	7	7	14
Measles	1	3 (3)	4 (3)
Mycoplasma pneumonia	2	1	5 (2)
Cytomegalovirus	1	0	1
Total deaths	(1)	(3)	(6) (4%)

*Deaths from infection in parenthesis

Table 5 *Factors influencing disease free survival*

	p Value	*Stratified for white blood cell count*
Presenting leucocyte count	0 001	
Franco-American-British subtype	0 004	(0 01)
Age*	0 02	(0 05)
Phenotype*	0 021	(0 2)
Spleen size	0 07	(0 2)
Sex	NS	
Liver size	NS	
Lymph nodes	NS	
Haemoglobin	NS	

NS=Not significant
*p=Value for heterogeneity

Discussion

The protocol was in general well tolerated with a low morbidity. The addition of daunorubicin to prednisolone and vincristine during induction did not increase the incidence of serious infection in comparison with our previous series[6] and no adverse side effects were observed during the four week course of subcutaneous L-asparaginase. The choice of a semi-continuous regimen for continuing maintenance treatment was based on our own observations,[7] confirmed in the MRC UKALL V protocol,[8] that this type of schedule was as effective as the more conventional continuous regimen but less immunosuppressive. This is reflected in the fairly low incidence of serious infections during treatment The continuing risk of measles remains, as we have previously reported, a cause for serious concern.[9]

Plasma methotrexate concentrations are extremely variable after oral administration and may be influenced by the timing and content of meals. While we attempted to standardise the time of methotrexate dose to achieve maximum plasma concentrations, we also suspected that giving the drug by injection might reduce the risk of bone marrow and testicular relapse. We were unable to show any benefit, however, for the intramuscular route, which was associated with a higher incidence of remission deaths, particularly in the low risk patients. The two deaths in patients on oral methotrexate who were not randomised occurred in patients with Down's syndrome, a group more at risk in view of their existing immunodeficiency.

Patients with T cell acute lymphoblastic leukaemia were not entered into the trial so that few patients had recognised adverse prognostic factors such as a leucocyte count in excess of $50\times10^9/l$. We have been unable, within the limitations of this small study, to determine any subgroup of patients for whom intramuscular methotrexate seemed to be superior.

These results are in apparent contradiction to those of the recently reported MRC UKALL VII trial,[10] a national study confined to standard risk patients (initial leucocyte count less than $20\times10^9/l$) that was conducted during the same period, but with many more randomised variables that could have affected the outcome, such as testicular irradiation, variable L-asparaginase during induction, and long term intrathecal methotrexate. Moreover, the methotrexate was given as a five day course every four weeks rather than weekly. In our trial, with similar numbers of standard risk patients, the route of administration of methotrexate was the only variable and proved to have no demonstrable effect on outcome. The factors influencing prognosis remained the traditional ones of age and leucocyte count. After stratification for these factors the morphological classification retained its prognostic importance, but patients with null cell leukaemia fared no worse than those with common cell leukaemia.

Further analyses of toxicity and pharmacokinetics are in progress, but it is of concern that a number of children developed convulsions during or after treatment and that four children developed computed tomogram changes suggestive of leucoencephalopathy, a complication described regularly only in children receiving intravenous methotrexate at a higher dose than our patients.

Thus, in summary, this trial suggests that intramuscular methotrexate is no better, and in fact is probably more harmful, than oral methotrexate in continuing (maintenance) treatment of childhood acute lymphoblastic leukaemia

We thank the Leukaemia Research Fund and the Medical Research Council for support. This study would not have been possible without the organisational skills of Miss Jeanette Stevens

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Serological study of *Pneumocystis carinii* infection in the absence of immunosuppression

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SUMMARY Serum samples from 145 children with no known immunosuppressive illness were examined by indirect immunofluorescence for antibody to *Pneumocystis carinii*. Positive antibody titres (≥1:8 dilution) were found in 69 children (48%). Antibody could not be detected in the remaining children. Previous studies have shown that at least 75% of children have antibodies to *P. carinii* by the age of 4 years. This study shows a lower percentage of children with detectable antibody. This may be related to geographical variation of antigen or possibly to the widespread use of co-trimoxazole.

Pneumocystis carinii pneumonia occurs almost exclusively in the immunocompromised host. Isolated *P. carinii* organisms have been identified, however, in the lungs of individuals with no evidence of disease.[1] It is thought that clinical infection occurs as a result of reactivation of latent organisms producing replication and subsequent disease. There have been problems encountered in the development of specific methods for detecting infection histologically and serologically and these have caused the reliability of serological diagnosis in particular by either complement fixation or indirect immunofluorescence to be questioned.

Previous studies have suggested that there is a high prevalence of latent infection, with almost 100% of normal children tested in a Dutch study having positive antibody by the age of 2.[2] A similar study carried out by Pifer *et al* found that by the age of 4 years two thirds of normal children had antibody to *P. carinii* in titres of 1:16 or greater.[3] Both of these authors concluded that their results indicated subclinical infection was highly prevalent in normal children but that disease was manifested in the compromised host only.

As part of a prospective study of pneumocystis antibody titres in children with acute lymphoblastic leukaemia we wished to find whether these observations applied to non-immunosuppressed children in the United Kingdom.

Patients and methods

Serum samples from 145 children were studied. Specimens were obtained at the same time as other routine blood tests from children attending the diabetic clinic at the Royal Victoria Infirmary, Newcastle (50 children), and from children attending the paediatric outpatient clinics at the Royal Hospital for Sick Children, Edinburgh (95 children). The latter group comprised children attending the cardiology and haematology departments. No child was known to be suffering from any immunosuppressive illness and none was on steroid medication. The age range was 0·45 to 13·9 years (mean 7·4 years and median 7·35 years). There were 82 boys and 63 girls in the study.

Serum samples were tested at the microbiology department of the Royal Marsden Hospital, London, using an indirect immunofluorescence test, full details of which have been reported previously.[4] Briefly, the substrate used was a paraffin section of human lung heavily infested with pneumocysts The tissue was fixed in Bouin's fluid to destroy existing immunoglobulin in the alveolar exudate and to preserve polysaccharide antigen. The serum samples were initially screened at a 1:8 dilution with fluorescein labelled antihuman immunoglobulin (Wellcome reagents). Positive samples were subsequently titrated for IgG antibodies in doubling dilutions from 1:8 upwards. A positive reading was recorded when the entire content of the alveolar spaces (which include all stages of the parasites' development) was brightly stained.

Results

Seventy six children (52%) had no detectable antibody to *P. carinii*. Thirty six, 19, and 14 (25%,

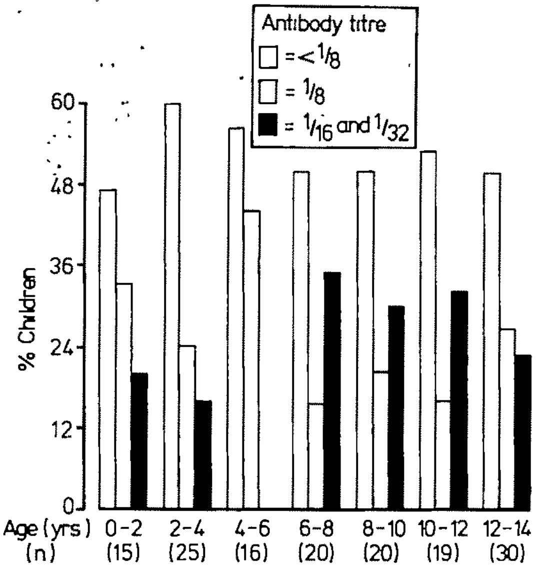

Figure *Pneumocystis antibody titres at different ages.*

13%, and 10%) had antibody present at dilutions of 1:8, 1:16, and 1.32, respectively. The results were analysed to observe any variation in antibody production with age, and these calculations are shown in the Figure. There was a trend to more of the older children having higher levels of antibody but this did not achieve significance

Discussion

These findings conflict with the earlier studies by Meuwissen[2] and Pifer.[3] Studies using axenic rats have shown that *P. carinii* is naturally acquired as an airborne organism in a de novo infection.[5] *P. carinii* seems to be a widely prevalent organism, but geographic variations in its distribution may occur and this could explain the different results obtained in this study, which was carried out in children from the north of England and Scotland in the autumn of 1984, and the two previous studies, which were carried out in Dutch children in 1977 and in children from Memphis, Tennessee, in 1978.

Co-trimoxazole is a commonly used antibiotic in the UK and is often used in the treatment of upper and lower respiratory tract infections. The use of prophylactic co-trimoxazole is effective in preventing pneumocystis pneumonitis in children immunosuppressed as a result of acute lymphoblastic leukaemia.[6] The widespread use of this antibiotic within the community could possibly reduce the number of primary infections that occur, and this could explain the different results obtained. In contrast co-trimoxazole has not been widely used in general practice in the United States until fairly recently.

The incidence of *P carinii* pneumonitis is difficult to ascertain. A study from the USA by Siegel *et al* found an incidence of *P. carinii* pneumonia of 6·8% in a group of 844 children undergoing treatment for acute lymphoblastic leukaemia.[7] Darbyshire *et al* in a report from the UK documented an incidence of proven *P. carinii* pneumonitis of 9% in a group of 199 children with acute lymphoblastic leukaemia.[8] Thus it would seem that there is no great difference in the incidence of pneumonitis due to pneumocystis in the immunocompromised children from the USA and UK despite the different distribution of antibody titres in the population.

All three studies used an indirect immunofluorescence method for the detection of antibodies This study used human lung heavily infested with pneumocysts. The method of extraction was designed to destroy existing immunoglobulin in the alveolar exudate and preserved polysaccharide antigen. In contrast Pifer *et al* used cysts grown in embryonic chick epithelial lung cell culture [3] The cysts were harvested and purified on a sucrose density gradient. Meuwissen *et al* also used human lung tissue as the slide antigen,[2] but there were differences in the purification and extraction of the material. These differences in methodology may have affected the sensitivity and specificity of the detection of *P. carinii* antibody and could account for the different results obtained.

This study was performed to define the distribution of *P. carinii* antibody in the UK child population as a prelude to a study in children with leukaemia. Initial results from the study on leukaemia show a very similar distribution of *P. carinii* antibody titres at the time of diagnosis as occurs in this 'normal' group Thirty nine out of 85 (47%) children with leukaemia below the age of 4 years had no detectable antibody. Over the age of 4 years 41 out of 78 children (47%) were also antibody negative. Further studies on this group of children with acute lymphoblastic leukaemia are in progress and will be reported later.

We are very grateful for the expert technical help given by Mrs J Skilton and Mrs M J Renton We would also like to acknowledge the help of Drs S Court and J M Parkin in allowing specimens to be collected from children under their care

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British Paediatric Association

Annual meetings

At York University:
1987 April 7–10
1988 April 12–16
1989 April 11–15

At University of Warwick:
1990 April 3–7
1991 April 16–20
1992 April 7–11
1993 April 19–23 (provisional)
1994 April 11–15 (provisional)

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Ten minute radiopharmaceutical test in biliary atresia

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SUMMARY To provide an objective rapid means of excluding extrahepatic biliary atresia (atresia), a hepatic index was devised from the ratio of the net hepatic to cardiac distribution of ^{99m}Tc diisopropyl iminodiacetic acid or methylbrom iminodiacetic acid between 2·5 and 10 minutes after injection. The hepatic index was compared with subjective assessment of abdominal scintigraphy performed repeatedly over 24 hours. In 22 infants with hepatitis the hepatic index ranged from 5·03 to 14·9, one having no excretion on scintiscan. In 26 infants with atresia the index ranged from 0·49 to 4·26 and in two with paucity of intralobular bile ducts it was 1·85 and 3·69. None of these infants had excretion apparent on scintiscans. Similarly, low hepatic indices occurred in four infants with liver dysfunction but pigmented stools, three of whom had no excretion apparent on scintiscans. These preliminary studies suggest that a hepatic index of greater than 5 is much more rapid and as specific in excluding atresia as repeated abdominal scintigraphy.

Over 70% of infants with extrahepatic biliary atresia (atresia) become free of jaundice after portoenterostomy if the operation is performed in the first eight weeks of life[1] Ninety per cent of those who lose their jaundice are thriving at 10 years of age.[2] Accurate pre-laparotomy differentiation of atresia from intrahepatic disorders that cause severe cholestasis is essential if the correct infants are to be selected for this radical operation. Findings on laparotomy may be misleading in up to 20% of infants, with the danger of inappropriate removal of small, narrow, but patent bile ducts in infants with intrahepatic disease.[3 4] Radiopharmaceuticals, which are preferentially excreted into the biliary system and thereby show bile duct patency, provide important information for identifying infants who do not require laparotomy.

Recently, abdominal scintigraphy after intravenous administration of ^{99m}technetium diisopropyl iminodiacetic acid (DISIDA) in infants pretreated with phenobarbitone has replaced the ^{131}I Rose-Bengal faecal excretion test as it is as accurate and much more convenient.[5] There are three major problems in interpreting abdominal scintiscans. Firstly, the decision whether the isotope is in the kidneys or gall bladder or in the urinary bladder or bowel is entirely subjective. Secondly, in those infants with severe intrahepatic cholestasis and slow excretion the radiopharmaceutical may only enter the bowel after 12, 18, or 24 hours, by which time it is often not detected as most of the radionuclide has decayed. Thirdly, the test is also time consuming as it requires repeated scans at intervals from 20 minutes after injection up to 24 hours. To overcome these difficulties we have developed a technique that is objective, avoids confusion caused by urinary excretion of the isotope, and is based on the tissue distribution of the radiopharmaceutical in the first 10 minutes after intravenous injection.

Patients

A total of 54 infants with jaundice aged 3–16 weeks were studied between December 1983 and December 1985. Fifty infants aged 3–12 weeks had acholic stools and were considered to be possible cases of atresia Final diagnoses were: 26 cases of atresia, 17 of idiopathic hepatitis of infancy, five of α_1 antitrypsin deficiency, and two of paucity of the interlobular bile ducts (biliary hypoplasia) The diagnosis of atresia was confirmed by histological examination of the biliary remnants removed at portoenterostomy α_1 Antitrypsin phenotyping was determined by isoelectric focusing[6] Diagnosis in other cases was made by excluding known causes of liver damage in this age group, by histological assessment of percutaneous liver biopsy specimens, and by the patient's subsequent course.[7]

At the time of study the mean values of standard biochemical tests of liver function, serum bilirubin concentration, aspartate aminotransferase, γ-glutamyltranspeptidase, and alkaline phosphatase activities were not significantly different in those with atresia and those with intrahepatic disease.

To investigate the specificity of our findings and clarify mechanisms responsible the investigation was performed in four further infants who had bile pigmented stools and thus were not suspected of having atresia. Two had idiopathic fulminant hepatic failure, one was recovering from portal pyaemia, and one had liver disease associated with panhypopituitarism. Informed consent was obtained from the parents.

Methods

Development of the hepatic index. After at least three days of oral phenobarbitone in a dose of 5 mg/kg/day[8] 37 mBq of ^{99m}Tc DISIDA (Disofen, New England Nuclear Chemicals Ltd) was given intravenously. The infant was placed for 10 minutes over an International General Electric (535) gammacamera linked to an Analog Data Analysis Company computer system. Gamma emissions were recorded continuously in 30 second frames.

One 30 second recording was subsequently displayed on a television monitor and, using the computer linked pen, areas were defined within the outline of the liver, heart, and lung fields (representing background activity) (Fig. 1). The counts in these areas were analysed in all 30 second frames, corrected to unit area, and depicted as an activity/-time curve, giving the count density over the liver, heart, and background as a function of time. Analysis of these curves in 19 infants, 11 of whom had atresia, showed that complete separation of patients with atresia from those with intrahepatic disease could be obtained from frames between 2·5 and 10 minutes after injection on the basis of the ratio of the net counts over the liver and heart. This ratio, counts over liver minus counts over background divided by counts over heart minus counts over background during this 7·5 minute period, we termed the hepatic index.

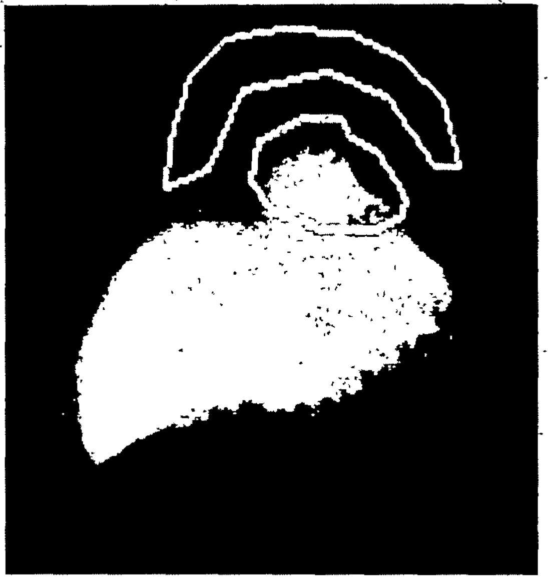

Fig. 1 *Black and white photograph of the representation in colour on the video screen of the gamma irradiation in one 30 second frame· Areas of interest within the outlines of the liver and heart and an area encircling the heart representing background activity have been drawn with a computer linked light pen*

Prospective study. The hepatic index was applied prospectively in 35 infants. In these studies the derivative of iminodiacetic acid ^{99m}technetium trimethylbrom-IDA (TMB-IDA) (Sorin Biomedica SPA) was used as DISIDA was withdrawn temporarily from use in the United Kingdom. TMB-IDA

Table *Hepatic index and subjective assessment of isotope excretion in abdominal scintiscans after intravenous ^{99m}technetium iminodiacetic acid (DISIDA and TMB-IDA)*

Disorder	*No of cases*	*Hepatic index*		*Scintigraphic findings of intestinal radioactivity*	
		Range	*Mean (SD)*	*Absent*	*Present*
Biliary atresia	26	0·49–4·26	2·59 (0·19)	26	—
Idiopathic hepatitis of infancy	17	5·03–12·27	8·31 (0·62)	1	16
Hepatitis with α_1 antitrypsin deficiency	5	7·2 –14·19	9·8 (1·4)	-	5
Paucity of interlobular bile ducts	2	1·85		1	—
		3·69		1	—
Fulminant hepatic failure	2	0·80		1	—
		3·76		1	—
Portal pyaemia	1	2·30		—	1
Panhypopituitarism	1	1·34		1	—

had the advantage of improved hepatic uptake and less renal excretion.[9]

Results

The hepatic index and the results of the conventional 24 hour ^{99m}technetium iminodiacetic acid (DISIDA and TMB-IDA) abdominal scintigraphy in all 54 infants are given the Table. In patients with atresia the hepatic index ranged from 0·49 to 4·26 (mean (SD) 2·59 (0·19)). None had isotope excretion into the bowels even at 24 hours. The hepatic index in infants with cholestasis with idiopathic hepatitis or α_1 antitrypsin deficiency ranged from 5·03 to 14·19. All showed isotope excretion into the bowels within four hours except one infant with idiopathic hepatitis in whom no excretion occurred even at 24 hours. The hepatic index in this infant was 5·03. No isotopic activity was detected in the bowels of two infants with paucity of intrahepatic bile ducts. Their hepatic indices were 1·85 and 3·69.

Two infants with fulminant hepatic failure and one with panhypopituitarism also had low hepatic indices (1·85, 3·69, and 1·34, respectively) No bowel radioactivity could be detected in these infants and all had markedly reduced hepatic uptake. The infant recovering from portal pyaemia also had a low hepatic index of 2·3 but bowel radioactivity was evident at seven hours. This infant, too, had markedly reduced hepatic uptake. The comparison of the hepatic index and hepatic uptake (Fig. 2) showed that when the index was greater than 5 there was a high uptake of the radiopharmaceutical, whereas when the index was less than 5 the uptake was reduced. There was no significant relation beween the hepatic index and net cardiac counts.

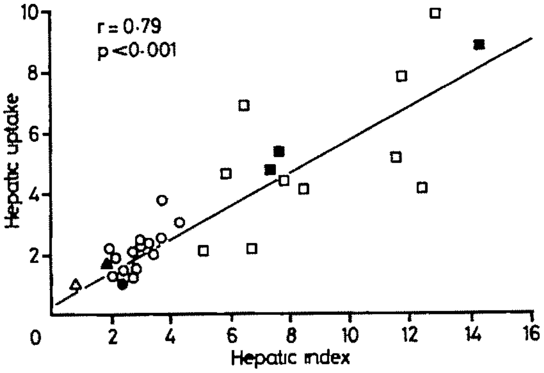

Fig 2 *The relation between hepatic index and hepatic uptake (the ratio of net hepatic counts to background counts) in 30 infants.* ○=*Biliary atresia;* □=*idiopathic hepatitis of infancy;* ■=*hepatitis with α_1 antitrypsin deficiency;* ●=*portal pyaemia,* △=*fulminant hepatic failure;* ▲=*paucity of intrahepatic bile ducts*

Discussion

Without effective surgery the mean age at death of patients with atresia is 11 months.[10] Portoenterostomy by an experienced surgeon produces bile drainage in up to 90% of infants if performed by 8 weeks of age (90% of those free of jaundice remain well at 10 years[1]) and survival until the third decade has been documented.[11] In contrast, infants with intrahepatic disease have a much better natural history, often making a complete recovery unless associated with genetic or familial disorders or paucity of the intrahepatic bile ducts [12] [13] If, however, such infants with complete cholestasis are submitted to laparotomy and cholangiography, even by experienced surgeons, inappropriate radical surgical procedures may be performed.[4] It has been our practice to submit to laparotomy infants with histological features in percutaneous liver biopsy specimens that are indicative of bile duct obstruction, unless the patient has been shown to have some genetic abnormality, such as α_1 antitrypsin deficiency or cystic fibrosis, or if syndromic paucity of the interlobular bile ducts or bile duct patency has been shown with radiopharmaceuticals.[7] In a recent study of 32 infants with severe cholestasis we have found that DISIDA scintigraphy performed after treatment with phenobarbitone was as efficient in showing bile duct patency as ^{131}I Rose-Bengal faecal excretion.[5] As the latter test takes at least three days and makes heavy demands on nursing time we no longer use it.

DISIDA and TMB-IDA are rapidly taken up by the liver and have low but appreciable renal excretion in infants with cholestasis. ^{99m}Technetium has good imaging properties but its short half life of six hours makes assessment of scintiscans difficult after 12 hours. Other authors have evaluated clearance from the blood and hepatic uptake in an effort to overcome problems caused by renal excretion of the radiopharmaceutical and short half life of ^{99m}technetium.

Gerhold and coworkers, in a study of 16 infants with atresia and 11 with hepatitis using DISIDA and diethyl IDA, used an entirely subjective method of grading clearance from the blood.[14] Patients with no visible cardiac radioactivity after five minutes had a numerical score of 1, while if there was considerable retention in the circulation, with the cardiac activity equalling or exceeding the hepatic activity by five minutes, a score of 4 was given. These authors found that patients with atresia had low scores and those with hepatitis higher scores but that there was considerable overlap between the two groups.

Kirk and coworkers, in a study of 15 infants with cholestasis using DISIDA, analysed 12 images taken in the first hour and five taken in the subsequent 23 hours.[15] They found that in infants with hepatitis and severe hepatocellular damage uptake into the liver was delayed, while in infants with atresia the uptake was normal Again the assessment was subjective

Bourdelat and coworkers, in a study of eight infants, three of whom had atresia, used diethyl IDA scintographic images to generate time/activity curves.[16] They also concluded that a good hepatic uptake was suggestive of atresia. The single time/activity curve given, however, showed that in the early stages the opposite was true Lennard *et al*, using diethyl IDA, subjectively analysed time/activity curves obtained over 60 minutes in six infants with atresia and 11 with hepatitis and found no appreciable hepatic uptake in patients with hepatitis but good hepatic uptake in patients with atresia.

In our studies using both DISIDA and TMB-IDA we found the opposite. In those patients with a cholestatic syndrome that was clinically indistinguishable from atresia the hepatic index was more satisfactory in those with hepatitis than in those with atresia. This may be due to differences in the patient population studied, treatment with phenobarbitone beforehand, or the hepatic extraction of the radiopharmaceuticals used. They are more likely to have arisen, however, because our study concentrated on the very early hepatic uptake and was entirely objective.

The cause of the slow hepatic uptake in patients with atresia is unclear. The clinical and pathological features in infants with hepatocellular damage associated with α_1 antitrypsin deficiency are often indistinguishable from infants with atresia, but the hepatic index in the patients with α_1 antitrypsin deficiency was similar to that in other types of intrahepatic disease. The low hepatic indices found in the patients with fulminant hepatic failure with a prothrombin time prolonged by more than 40 seconds at the time of the study was not surprising in that severe hepatocellular failure was present. The low hepatic index found in the patient during the recovery phase was from portal pyaemia and the infant with panhypopituitarism is unexplained.

Knodell and coworkers studied the effects of cholestasis on hepatic uptake of ^{99m}technetium *p*-isopropyliminodiacetic acid in isolated rat hepatocytes from animals with bile duct ligation or intrahepatic cholestasis induced by ethinyl oestradiol.[18] Decreased hepatic uptake occurred in both groups but was more pronounced in those with mechanical obstruction. The authors concluded that the decreased hepatic uptake might be attributable to higher bile salt concentrations but did not in fact measure these

From the point of view of clinical management, the low hepatic index in the two infants with syndromic paucity of interlobular bile ducts is particularly disappointing as such infants may have severe cholestasis in infancy and some have liver biopsy features compatible with bile duct obstruction in the first six months of life. The non-hepatic features of this syndrome are not sufficiently specific in all cases to make a diagnosis before laparotomy.[7] At laparotomy the extrahepatic ducts are often so small that cholangiography performed through the gall bladder may fail to fill the intrahepatic ducts. Such infants are at great risk of inappropriate surgery.[4] These preliminary studies suggest that a hepatic index of 5 or more in this 10 minute investigation is as discriminating and specific in excluding infants with extrahepatic biliary atresia as repeated abdominal scintigraphy over 24 hours. Where the hepatic index is less than 4·3 atresia is a strong possibility but the result must be considered in the light of other clinical and investigative findings.

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Iron deficiency in cystic fibrosis

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SUMMARY Iron state was measured as part of the comprehensive assessment of 165 patients with cystic fibrosis. Of 127 patients, 41 (32%) had low serum ferritin concentrations and at least this proportion were iron deficiency.

Iron state did not correlate with clinical score, radiological score, or results of sputum culture. There was no evidence that patients with iron deficiency were either in better or worse clinical condition than those with better iron stores.

As survival improves in cystic fibrosis the importance of good nutrition becomes increasingly apparent. Careful attention to details of diet and to dietary supplementation is routine in most cystic fibrosis centres.

Iron supplements are not generally considered necessary and are not usually provided It is widely believed that individuals with malabsorption secondary to pancreatic insufficiency do not become iron deficient; current paediatric opinion suggests that in cystic fibrosis 'because of the abnormally low pH of the upper jejunum, the absorption of iron is enhanced'.[1] There are similar statements in other paediatric textbooks.[2] In addition, there is concern that iron may encourage bacterial infection.[3]

One hundred and sixty five patients with cystic fibrosis underwent comprehensive assessments of their clinical state in our unit. Their serum ferritin concentrations were compared with their general clinical scores, chest radiograph scores, and the presence of pseudomonas infection. We also report their haematological data.

Methods

Details of the comprehensive assessments of patients with cystic fibrosis performed at this centre have been reported[4] The relevant results from the first complete assessment for each patient are presented. None of the subjects was receiving iron supplements at the time of assessment

The assessment included a full history, physical examination, and chest *x* ray films The Shwachman clinical score[5] and Chrispin-Norman chest *x* ray score[6] were calculated.

Sputum was cultured at the assessment and results of previous cultures obtained. Patients were classified according to whether pseudomonas was grown regularly (Y), had previously been grown intermittently (I), or had never been grown (N).

A fasting blood sample was taken. Haemoglobin and mean corpuscular volume were measured by Coulter counter Serum ferritin concentration was measured using an in house method, a polyethylene glycol accelerated, post-precipitated, double antibody radioimmunoassay, a modification of the method of Luxton *et al.*[7] The samples were batched for this measurement. Serum ferritin concentrations of less than 12 ng/ml represented reduced or absent iron stores.[8]

Comparison was made with clinical state, changes on chest *x* ray film, and chest infection by calculating Spearman rank correlation coefficients between serum ferritin concentration and Shwachman score, Chrispin-Norman score, and the presence of pseudomonas chest infection, respectively. In view of the progression of the disease with age, the coefficients were calculated separately for each age group.

Table 1 *Serum ferritin concentration by age in the 127 patients with cystic fibrosis studied*

Age in completed years	*Not measured*	*Serum ferritin*	
		≥12 ng/ml	*<12 ng/ml*
0	1	6	1
1, 2	6	16	5
3, 4	4	11	7
5–7	6	10	11
8–10	9	15	7
11–15	6	12	6
16+	6	16	4
Total (No (%))		86 (67 7)	41 (32 3)

Table 2 *Shwachman score, chest x ray score, and presence of pseudomonal chest infection by age in patients with cystic fibrosis*

Age in completed years	*No*	*Shwachman score*		*Chrispin-Norman score*		*Pseudomonas infection*		
		Range	*Median*	*Range*	*Median*	*N*	*I*	*Y*
0	8	70–100	95	0–6	1	8	0	0
1, 2	27	55–100	85	0–9	2	24	1	2
3, 4	22	40–100	85	0–11	3	18	2	2
5–7	27	40–100	80	1–25	7	20	0	7
8–10	31	45–90	75	0–20	7	20	0	11
11–15	24	30–95	72 5	2–27	9	9	4	11
16+	26	40–95	60	3–23	14	11	0	15

N=Pseudomonas absent; I=pseudomonas intermittently grown, Y=pseudomonas present
For Shwachman score, higher score=better clinical state, for Chrispin-Norman score, higher score=worse chest *x* ray

Results

There were 78 boys, aged 9 weeks to 25 years 7 months (median 8 years 5 months), and 87 girls, aged 24 weeks to 30 years 2 months (median 8 years). No sex differences emerged for any of the variables studied.

Serum ferritin concentration was less than 12 ng/ml in 41 of the 127 patients studied (32%) (Table 1). These patients were distributed evenly throughout the age range.

Three of 161 patients (2%) had a haemoglobin concentration less than 11 g/dl and 14 (9%) between 11 and 12 g/dl. Mean corpuscular volumes were less than 75 fl in eight (5%) and between 75 and 80 fl in 32 (21%) of 153 patients.

All variables of clinical state gradually worsened with increasing age. The Shwachman score declined, the Chrispin-Norman score rose, and there was an increase in the incidence of pseudomonas chest infection (Table 2). At all ages, however, there were patients whose clinical state was good.

There was no correlation between serum ferritin concentration and Shwachman score, Chrispin-Norman score, or presence of pseudomonas infection.

Discussion

A total of 32% of our patients had low serum ferritin concentrations, a finding that conflicts with generally accepted teaching concerning iron state in cystic fibrosis but that supports the findings of Ater *et al*,[9] 13 of whose 39 patients (33%) had a serum ferritin concentration below 12 ng/ml.

In the assessment of iron deficiency a serum ferritin concentration of less than 12 ng/ml represents reduced or absent iron stores, whatever other complications are present.[8] High serum ferritin concentrations are found in inflammation, common in patients with cystic fibrosis, so that 32% is a minimum estimate of the incidence of poor iron state in patients with cystic fibrosis from Yorkshire.

Many of our patients may well have had a relative anaemia, in view of their poor pulmonary state.[9]

Cystic fibrosis is a serious disease in which premature death is commonly caused by the effects of repeated chest infections. It is almost certain that nutritional problems, which are common, contribute considerably to morbidity and mortality, and it would be logical to attempt to correct deficiencies, possibly including iron deficiency.

There has been much discussion, however, of the relation between iron state and bacterial infection In vitro, bacteria such as *Escherichia coli* grow and multiply under iron rich conditions,[3] although iron saturation in vivo may not have the same effect on bacterial growth and multiplication.[10] On the other hand, reduced immunological resistance to bacterial infection has been seen in iron deficiency,[3] and in rats iron deficient diets reduce thymic and splenic growth and differentiation.[11]

The relevance of such experimental work to humans is unclear. Catastrophic effects of iron supplementation—namely, lethal bacterial infections—have followed the use of prophylactic parenteral iron in newborns from a population thought to have severely compromised nutrition and to be at risk of multiple deficiencies [12] Acute pseudomonal pyelonephritis is not enhanced, however, by treatment with iron.[13]

There are indications that mucoid *Pseudomonas aeruginosa* is the most stable strain under iron limited conditions[14] and that emergence of the mucoid strain so common in patients with cystic fibrosis is favoured by iron restricted conditions in the lung.[15]

We found no evidence at any age of a correlation between higher serum ferritin concentration and worse clinical state, more severe chest involvement, or the presence of pseudomonas chest infection. Neither did we find any correlation between these variables and lower serum ferritin concentration.

Our approach to management is to strive for physiologically 'normal' variables, wherever possible, and our patients receive aggressive dietary management and vitamin supplementation. In view of the conflicting and confusing evidence about iron state, particularly regarding bacterial infection, we propose a trial of iron supplementation for our patients with cystic fibrosis who have iron deficiency.

Thanks are due to the patients and their families and to the staff of the unit and the hospital. We are grateful to Keith Gailer for performing the serum ferritin assays

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Short reports

Colorectal polyps: an important cause of rectal bleeding

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SUMMARY Seventy one children with rectal bleeding were examined by total fibreoptic colonoscopy. Large bowel polyps were found in 45; 27 (60%) had solitary rectal polyps. Altogether, 83% of resected polyps were juvenile No complication of colonoscopic polypectomy occurred New polyps reoccurred in four (9%) treated children

Rectal bleeding is an alarming symptom in children but often not life threatening. Colorectal juvenile polyps may be a common cause of rectal bleeding in the preadolescent age group. Although polyps may often undergo auto-amputation, profuse bleeding or malignancy may sometimes occur.[1–3] Colocolic invagination, rectal prolapse, massive rectal bleeding, or recurrent abdominal pain may complicate non-resected polyps. A recent case of large bowel carcinoma complicating juvenile polyps showed the need for a more stringent diagnostic and therapeutic approach.

From 1981 to 1986, 71 children with rectal bleeding were studied by means of total fibreoptic colonoscopy. Large bowel polyps were diagnosed in 45 children (63%); all were resected during colonoscopy. Details of investigation, treatment, and follow up of children with colorectal polyps are presented.

Patients and methods

Seventy one children with recent lower gastrointestinal bleeding were investigated by total colonoscopy. Their mean age was 7·3 years (range 8 months to 16 years) The patients were admitted to hospital on the day before examination. The methodology of Williams *et al* was used for bowel preparation, sedation, instrumentation, and the technique of total colonoscopy.[3] Blood was cross matched and available before polypectomy. An adult Olympus colonofibrescope CF-LB3, Olympus electrosurgical unit PSD-2, and MTW polypectomy snares (Wesel, West Germany) were used. The duration of the colonoscopy was not more than 30 minutes. After polypectomy the children were observed for 24 hours and then discharged.

Results

The diagnoses of the 71 patients are summarised in Table 1. Large bowel polyps were found and resected in 45 children (63%); 27 (60%) had solitary rectal polyps. They were mostly 10–12 mm in diameter and easy to snare and resect. Table 2 summarises the distribution of the polyps. Of the resected polyps, 83% were juvenile and 8% inflammatory. In addition, one adenomatous, one Peutz-Jeghers, and two right colonic lymphoid

Table 1 *Colonoscopic diagnosis of rectal bleeding in 71 patients*

Diagnosis	*No (%)*
Polyps	45 (63)
Ulcerative colitis	13 (18)
Follicular and nodular lymphoid hyperplasia	2 (3)
Hemangioma	2 (3)
Unknown cause	9 (13)

Table 2 *Distribution and numbers of polyps in 45 patients with large bowel polyps*

Site of removal	*No of polyps*	*No of patients*
Rectum	1	27
Rectum	2	2
Rectum and sigmoid colon	2	2
Rectum and descending colon	2	1
Rectum, sigmoid and transverse colon	3	1
Sigmoid colon	1	5
Sigmoid colon	2	1
Ascending colon	1	1
Caecum	1	1
Polyposis		
Juvenile	15	1
	90	1
	Many	1
Inflammatory	Many	1
Total		45

*Many=Too many to count

polyps were resected. One child with a bleeding juvenile polyp was also found to have ileal nodular lymphoid hyperplasia, and two children with ulcerative colitis in remission bled from juvenile polyps in the rectum and sigmoid colon.

No complications arising from polypectomy were encountered. New polyps (three in the rectum and one in the sigmoid colon) occurred in three children after a minimum of eight months).

Discussion

This study shows that colorectal polyps may be responsible for a surprisingly large proportion of cases of rectal bleeding in childhood, particularly where the incidence of inflammatory bowel disease is not high.[1–6] It also confirms the value of total colonoscopy in investigating children with lower bowel bleeding; digital examination, single contrast barium enema, and proctoscopy alone are insufficient. We have abandoned the use of large bowel radiology in our hospital because of the superiority of colonoscopy in detecting polyps. We were unable, however, to compare the diagnostic values of these methods in children.

Bleeding from the lower gastrointestinal tract may have two simultaneous causes in one child: ileal nodular or follicular lymphoid hyperplasia. Colorectal polyps were seen in two patients with quiescent ulcerative colitis. Failure to detect the polyps could have led to a wrong diagnosis that the inflammatory bowel disease was in relapse.

Histology of resected polyps showed that juvenile polyps predominated, as has been found in previous studies.[1–6] The finding of a large bowel adenoma in a 2 year old boy is particularly important as such lesions can be premalignant. Thus the removal of all large bowel polyps in children as well as in adults is essential, even in the case of histologically confirmed juvenile polyps.

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Hearing loss due to mumps

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SUMMARY The possibility of mumps was considered in 33 children with profound unilateral sensorineural hearing loss of unknown origin. Fifteen gave a history of mumps, of whom 12 contracted the infection between the last normal and first abnormal hearing tests. Hearing should be tested after mumps infection.

The epidemiology of mumps in England and Wales is reported to be changing from an epidemic disease of young adults and older children to a more endemic disease affecting younger age groups, with an associated change in the age distribution of general practitioner consultations.[1] Although the incidence of recognised clinical disease may be falling, mild and symptomless mumps infections are possibly more common. Complications of mumps may arise, irrespective of the severity of infection, and can occur in the absence of parotitis.[2]

Deafness is a widely recognised complication of mumps, characteristically unilateral and sensorineural in nature, and is thought to result from endolymphatic labyrinthitis.[2] The hearing loss is usually acquired suddenly, four to five days after the onset of illness, and results in permanent profound hearing impairment. The incidence of this complication has been regarded as rare, of the order of 0·05/1000 cases,[3] although unrecognised mumps can cause severe deafness.[4]

This study reports an investigation undertaken in

South Clwyd (with a population of roughly 55 000 aged 16 years or under[5]) to identify children who may have acquired profound unilateral sensorineural hearing loss as a result of mumps, to assess whether audiological assessment is indicated routinely after this infection.

Methods

Over a 12 month period a search was conducted of the audiological records of children aged 16 years or under in South Clwyd to identify known cases of severe (70 db or greater, across the range 250 to 8000 Hz) unilateral sensorineural hearing loss.

Using a prepared proforma, further information was obtained about individual cases from child health and school health records. Dates of the last normal hearing test and the first abnormal test, the degree of impairment, and the opinion of the consultant ear, nose, and throat (ENT) specialist concerning the aetiology of the defect were recorded. Information was sought about the birth and medical history and family history of deafness and if necessary clarified by contacting either the parents or general practitioner.

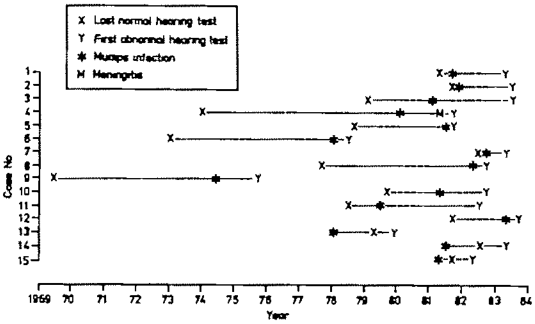

Figure *Timing of mumps infection in relation to normal and abnormal hearing test results in 15 cases with a positive history of mumps*

Table *Proposed aetiology of hearing loss given by the consultant ear, nose, and throat specialist for cases 1 to 15*

Case No	*Aetiology of hearing loss*	*Comment*
1–3	Mumps	Severe mumps infections reported
4	Meningitis	Profound hearing loss after meningitis
5–7	Congenital	Diagnoses of congenital hearing loss were made despite normal hearing tests previously
8–15	Inconclusive	No definite cause proposed

Results

Thirty six cases of profound unilateral sensorineural hearing loss were identified for whom normal hearing test results had previously been recorded. Three of these cases were excluded from further consideration, as hearing impairment was acquired gradually in one and essential information could not be obtained about the other two. Thirty three cases (19 boys and 14 girls) therefore formed the basis of this study, with acquired hearing loss of profound degree on first ascertainment

Records confirmed that each child had attended a consultant ENT specialist after the discovery of the hearing defect, previously normal hearing test results being available at that time The causes of hearing loss proposed in the consultant's letters written subsequently were mumps (three cases), meningitis (three), congenital (11), and inconclusive (16).

The interval between the last normal hearing test recorded and the first abnormal hearing test ranged from four months to six years two months, with a mean interval of two years five months In 12 cases (36%) more than three years had elapsed between the consecutive normal and abnormal hearing tests. A positive history of mumps was given by 15 of the 33 children, at ages varying from 2 to 10 years (mean 5 years 1 month and median 4 years 3 months), of whom 10 were boys. The date of mumps infection in each of these 15 cases is shown in the Figure in relation to the last date when normal hearing was recorded and the first date when the unilateral hearing loss became apparent. The Table indicates the opinion of the consultant ENT specialist concerning the cause of hearing impairment in cases 1–15

The temporal relation between mumps infection and loss of hearing suggested mumps as a possible aetiological agent in cases 1–12, although clinically meningitis was the most likely cause in case 4 Mumps was an unlikely cause in cases 13, 14, and 15.

Discussion

Unilateral hearing loss may be overlooked in young children and pass unrecognised without formal hearing testing. It is important to preserve optimum hearing in the unaffected ear and to advise parents to seek early medical advice if ear conditions arise. Conductive hearing defects, which are common in this age group, may result in considerable functional impairment if superimposed on established sensorineural loss.

Screening services for hearing vary considerably between districts. In South Clwyd routine screening is offered using distraction tests at 7 months and audiometric assessments at school entry and in alternate academic years until school leaving age. This would seem to give comprehensive coverage, but in practice variations arise: some tests are postponed due to illness or absenteeism and children screened at the beginning of one academic year may not be recalled until the end of the academic year when further testing is scheduled, an interval approaching three years A period of this duration could be of long term consequence for a young child with unrecognised unilateral hearing loss.

Our investigation indicated difficulty in attributing a cause for sensorineural hearing loss in many of the cases identified. In 11 the defect was described as congenital despite available evidence of previously normal hearing and in 16 no conclusion was reached. Delay in ascertainment of hearing impairment, which may have been unsuspected by parents, and the extent of credence given to hearing testing in the community by hospital staff are both factors that might hamper diagnosis.

Temporal evidence suggests that mumps could be considered as a cause in a third of the cases of hearing loss studied. Subclinical or unrecognised mumps may have occurred in other instances. Seven cases contracted mumps between 1 April 1981 and 31 March 1982, in association with a nationally observed periodic rise in incidence [6] The possibility that particular strains of mumps virus might be more prone to cause auditory damage requires consideration.

The incidence of hearing loss due to mumps is unclear as few studies are available, particularly in relation to young children. This investigation concludes that mumps could be considered more widely as an explanation for some cases of unilateral hearing loss and that a formal prospective study with serology is indicated. Meanwhile, the changing epidemiology of mumps to a milder illness of younger children, the fact that permanent hearing impairment can result from subclinical or unrecognised infections, and the importance of unilateral hearing loss in this age group are factors that confirm the need for regular screening of hearing. In addition, routine testing of hearing should be considered after a history of mumps, particularly in districts where a comprehensive screening programme is not available.

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Meningitis presenting as hypertension

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SUMMARY A 21 month old girl who presented with what seemed to be hypertensive encephalopathy is described. Although her encephalopathy resolved with antihypertensive treatment, subsequent investigations revealed haemophilus meningitis.

We report a case of a child with otherwise uncomplicated meningitis who presented with fever, systemic hypertension, and encephalopathy. The possible pathogenic mechanisms are discussed and the need to consider meningitis in the differential diagnosis of acute hypertension is emphasised.

Case report

A 21 month old girl was referred because of acute systemic hypertension associated with fever and drowsiness. There was no important history A maternal aunt had had unspecified renal disease. The present admission had been preceded by three days of coryzal symptoms with no systemic illness. On the morning of admission she developed fever associated with deterioration in conscious state. She vomited a single dose of oral antibiotic but had not received antipyretics.

On examination at this time she was drowsy but rousable, with a temperature of 37·5°C (from previously measured 39°C) and blood pressure 200/100 mm Hg. Peripheral pulses and perfusion were normal There was no evidence of dehydration. Mild neck stiffness was noted. The fundi were normal with no evidence of papilloedema There were no focal neurological signs, although there was generalised hypotonicity There was no peripheral oedema and urinalysis revealed a trace of protein, moderate ketones, and two epithelial cells There was a single cafe au lait spot. Abdominal examination yielded normal results Laboratory investigations revealed no abnormalities and included a haemoglobin concentration of 11·8 g/dl, white blood cell count 10×10^9/l, and normal creatinine and electrolyte concentrations. Chest *x* ray yielded normal results and blood and urine cultures were taken. On the basis of these features a provisional diagnosis of hypertensive encephalopathy was entertained and the hypertension was treated with frusemide 1 mg/kg and diazoxide 5 mg/kg (in divided boluses over 60 minutes). Over the subsequent 30 minutes her blood pressure fell to 150/80 mm Hg, and this fall in blood pressure was associated with an improved conscious state She was then transferred to our hospital.

On assessment after transfer her blood pressure was stable at 110/70 mm Hg. Blood pressure was equal in both upper and lower limbs. Her temperature remained raised at 38·8°C. Her conscious state had improved to appropriate verbal responses, although she remained irritable. Fundi were normal but neck stiffness was noted and there was mild peripheral weakness. There was no evidence of dysautonomia Repeat full blood count showed a haemoglobin concentration of 13·9 g/dl and a white blood cell count of 20×10^9/l with toxic changes. In view of the neck stiffness and now toxic blood film a lumbar puncture was performed, which showed a turbid cerebrospinal fluid under normal pressure with 7600 white cells/ml, 2400 red cells/ml, and Gram negative bacilli. She was begun on treatment with ampicillin and chloramphenicol and slightly restricted intravenous fluids

Throughout her hospital stay blood pressure remained within the normal range. Temperature and neurological examination became normal within 48 hours and remained so. Cerebrospinal fluid cultures grew *Haemophilus influenzae* type b. Serum creatinine, urea, and electrolyte concentrations were normal and renal ultrasound showed normal renal anatomy.

Discussion

This child is presented to illustrate an unusual presentation of acute meningitis. Although acute transient hypertension is known to occur in diseases associated with raised intracranial pressure,[1] the association with acute meningitis is not documented. There was no clear evidence in our patient for raised intracranial pressure. Her fundi were normal, there were no suggestive neurological signs, and cerebrospinal fluid was tapped at normal pressure on lumbar puncture. At the time of presentation her encephalopathy was considered to be secondary to systemic hypertension, and this seemed to be supported when her conscious state improved after treatment of the hypertension. The dose of diuretic that she received, however, may have resolved a raised intracranial pressure that was not clinically evident.

Whatever the specific pathophysiology, the hypertension in our patient does seem to have been associated with the haemophilus meningitis. There was neither evidence for nor treatment of extracellular fluid volume depletion. There was no suggestion of Riley-Day syndrome. Our investigations cannot, however, totally exclude renal disease or primary catecholamine excess, although neither seem probable.

The pathophysiology of meningitis involves diverse mechanisms that could produce a picture of hypertension and encephalopathy.

(1) The involvement of blood pressure regulatory centres from the hypothalamus and medulla.[2–4] For example, (a) ischaemia or hypoxia of medullary centres through blood flow alterations associated with inflammation or ischaemia produced by mechanical compression;[3–5] (b) increased blood volume through hypothalamic antidiuretic hormone mechanisms, although usually this would involve a longer time course;[5 6] (c) sympathetic overactivity through stimulation of brain stem or spinal centres in which there may be other evidence of autonomic malfunction, such as poor peripheral perfusion, tachycardia, or poor urine output.[5 6]

(2) Raised intracranial pressure, although this would usually be associated with vagal activity.[4]

(3) Some children may have an underlying idiopathic tendency to hypertension in stressful situations.[1]

It is not possible to delineate the exact mechanism of our patient's hypertension. Although mild raised intracranial pressure was possibly the predominant cause, this was certainly not detectable clinically apart from encephalopathy originally attributed to systemic hypertension The assumption that systemic hypertension in cases of meningitis is secondary to raised intracranial pressure is therefore questionable. It is also evident that meningitis should always be considered in the differential diagnosis of acute systemic hypertension, especially if this is associated with fever. This case also illustrates the potential benefit in treating hypertension even in acute neurological disorders, although this should always be performed cautiously [6]

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Phosphatidylglycerol in tracheal aspirates for diagnosis of hyaline membrane disease

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SUMMARY Lecithin:sphingomyelin ratio and phosphatidylglycerol were determined by a rapid, simple method in tracheal aspirates obtained from 132 newborn infants with respiratory diseases, sixty five of whom developed hyaline membrane disease. Phosphatidylglycerol determination was more sensitive (97%) than lecithin:sphingomyelin ratio, but their specificities were similar (76%).

A deficiency in the pulmonary surfactant is believed to cause hyaline membrane disease in newborn infants. Pulmonary maturity has been assessed by the analysis of the phospholipids in the hypopharyngeal[1] and tracheal[2] aspirates of newborn infants. The most widely used test is the lecithin: sphingomyelin ratio described by Gluck *et al*,[3] but this method is time consuming and affected by contamination of the specimen with blood or meconium.

As a consequence, several investigators have suggested that other phospholipids from surfactant and particularly phosphatidylglycerol (PG) should be studied.[4] PG is synthesised almost exclusively by lung alveolar cells so that there is no interference in assays by blood or meconium. Both one and two dimensional thin layer chromatography are commonly used to analyse PG. These methods are time consuming, however, and require extensive laboratory technician training.

In 1983 Garite *et al* described a new, rapid, simple, and reliable method to determine PG in amniotic fluid by a semiquantitative immunological slide agglutination test.[5] A complete assay can be performed in about 30 minutes.

We have applied and compared this test to the lecithin·sphingomyelin in the tracheal aspirate.

Patients and methods

Tracheal aspirates were obtained from 132 infants who were admitted to the intensive care unit for respiratory disease. Of these, 65 were diagnosed as having hyaline membrane disease after satisfying clinical and *x* ray criteria. The other 67 infants had other respiratory diseases—namely, transient tachypnoea of the newborn (30 cases), congenital pneumonia (six), amniotic fluid aspiration syndrome (11), and other respiratory diseases (20). The gestational ages of the infants ranged from 26 to 42 weeks (mean 33 weeks) and their birth weights from 645 to 4700 g (mean 2160 g). Samples were obtained during the first 24 hours after birth.

The lecithin:sphingomyelin ratio was determined using the method of Gluck *et al*[3] and PG testing by Amniostat-FLM[5] were performed on all samples. A lecithin:sphingomyelin ratio $\geqslant 2\cdot 0$ and a PG$\geqslant$++ or 2 µg/ml were interpreted as being 'positive' and as indicating fetal lung maturity and a lecithin:sphingomyelin ratio <2 and PG<++ were interpreted as being 'negative'.[2–5]

Results

The Table shows the results of the lecithin:sphin-

Table *Determination of lecithin sphingomyelin (L S) ratio and phosphatidylglycerol (PG) in tracheal aspirates obtained from 132 newborn infants with respiratory diseases*

	(n=)	*Results of determinations*			
		L S and PG negative	*L S and PG positive*	*L S negative and PG positive*	*L S positive and PG negative*
Infants with hyaline membrane disease	(65)	59	2	0	4
Infants without hyaline membrane disease	(67)				
Transient tachypnoea	(30)	2	25	2	1
Congenital pneumonia	(6)	1	4	—	1
Amniotic fluid aspiration syndrome	(11)	1	8	1	1
Other respiratory diseases	(20)	5	6	4	5
Total	(67)	9	43	7	8

gomyelin and PG determination in tracheal aspirates of the 132 newborn infants with respiratory diseases.

For 59 of the 65 newborn infants (91%) who developed hyaline membrane disease, the two tests correlated well with the criteria for hyaline membrane disease, but for six (9%) the results showed no correlation. In four of these six cases the lecithin:sphingomyelin ratio was ≥2 but the PG was absent, and for the other two cases both tests indicated fetal lung maturity.

For the 67 newborn infants who did not have hyaline membrane disease, both biochemical tests predicted pulmonary maturity for 43 of them (64%), but for the 24 others (36%) the results showed no correlation. This lack of correlation was particularly noticeable in these cases with other respiratory diseases (14 of 20), particularly when their gestational ages were less than 30 weeks (80% of the cases). The lack of correlation was not so pronounced, however, in the cases with transient tachypnoea (five of 30), congenital pneumonia (two of six), and amniotic fluid aspiration syndrome (three of 11).

Discussion

In most cases (102 of 132 (77%)) a good correlation was observed between the results of laboratory tests and the clinical and *x* ray criteria for hyaline membrane disease.

The correlation was better, however, for the newborn infants who had hyaline membrane disease (91%). James *et al*[6] reported that for babies who did not have hyaline membrane disease, and in particular transient tachypnoea, congenital pneumonia, or amniotic fluid syndrome, the determination of phospholipids in tracheal or gastric aspiration was of doubtful importance. In our study this was observed for other respiratory diseases, in particular when the gestational age of the newborn was very low, but not for transient tachypnoea, congenital pneumonia, or amniotic fluid aspiration syndrome.

For the results that did not correlate (23%), in 11 infants (8%) both biochemical tests differed from the clinical diagnosis. The specificities of lecithin: sphingomyelin ratio and PG determination were similar (76% and 77%, respectively) In 19 cases (14%) there was no correlation between the two tests, but the PG determination was more sensitive (97%) than the lecithin:sphingomyelin ratio (88%) and the results were unaffected by blood or meconium contamination.

In conclusion, the high sensitivity, specificity, rapidity, and simplicity of this assay makes PG determination a useful method for assessing the presence of PG in tracheal aspirates in newborn infants for diagnosis of hyaline membrane disease.

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Platelet thromboxane B_2 production in neonatal pulmonary hypertension

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SUMMARY Production of platelet thromboxane B_2, a stable metabolite of thromboxane A_2, was measured in seven newborn infants with pulmonary hypertension during the first day of life. Platelet thromboxane B_2 production was significantly lower than in 12 healthy controls but did not correlate with simultaneous blood gas values.

Persistent pulmonary hypertension of the newborn, characterised by pulmonary arterial vasoconstriction and right to left shunting at the level of the foramen ovale or ductus arteriosus, or both, is often associated with severe hypoxic disorders of the neonate.[1] The exact mechanisms leading to persistent pulmonary hypertension of the newborn are still largely unknown, although changes in prostanoid metabolism have been suggested.[2] Thromboxane A_2 is a potent proaggregatory and vasoconstrictory prostanoid produced and released by the platelets during aggregation.[3] It is rapidly metabolised to its stable breakdown product, thromboxane B_2 [3] To study synthesis of thromboxane A_2 in pulmonary hypertension production of platelet thromboxane B_2 during spontaneous clotting was measured in seven infants with persistent pulmonary hypertension of the newborn during the first day of life.

Patients and methods

Seven infants with persistent pulmonary hypertension of the newborn were studied with the approval of the local committee of ethics. The clinical data of these infants are presented in the Table. All infants needed ventilatory help and one patient (case 2) who had severe meconium aspiration syndrome subsequently died at the age of 4 days. The diagnosis of pulmonary arterial hypertension was based either on clinical and echocardiographic findings (cases 1 and 3–6) or on direct measurement of the pulmonary pressure (cases 2 and 7). An umbilical arterial catheter for monitoring of blood gas and fluid infusion was inserted in all infants. Twelve healthy control infants with comparable birth weights, gestational ages, and Apgar scores were similarly studied. The controls were selected randomly and were studied over the same period as the patients. No mother in the study had taken any drugs known to interfere with prostanoid synthesis during the 10 days before delivery.

A blood sample (2·0 ml) from the umbilical arterial catheter in the study infants and from a peripheral vein in the controls was drawn into a dry test tube. Blood was first allowed to clot spontaneously for 60 minutes at 37°C and serum was then separated and measured for thromboxane B_2 radioimmunologically, as previously described.[4] The results were expressed as nanograms of thromboxane B_2 per 10^6 platelets and were analysed using the Mann-Whitney rank sum test.

Results

The median serum thromboxane B_2 concentration in our patients was 0·23 ng/10^6 platelets (range 0·06–1·20 ng/10^6 platelets), which was significantly ($p<0{\cdot}02$) lower compared with the healthy controls at the same age (0·95 ng/10^6 platelets; range 0·61–1·65 ng/10^6 platelets). There was, however, no correlation between the production of platelet thromboxane B_2 and the simultaneous blood gas values.

Table *Clinical data on the seven newborn infants with persistent pulmonary hypertension*

Case No	*Birth weight (g)*	*Gestational age (weeks)*	*Apgar score*		*Clinical diagnosis*
			At one minute	*At five minutes*	
1	4810	41	2	4	Meconium aspiration syndrome
2	3860	39	4	7	Meconium aspiration syndrome
3	4390	40	7	8	Meconium aspiration syndrome
4	2300	37	5	8	Meconium aspiration syndrome
5	2910	36	7	8	Respiratory distress syndrome
6	2200	36	9	9	Respiratory distress syndrome
7	3400	39	9	9	Down's syndrome, idiopathic pulmonary hypertension

Discussion

Persistent pulmonary hypertension in the newborn has a multiple aetiology and occurs in a variety of neonatal disorders. There is considerable evidence that thromboxane A_2 is involved in at least some forms of pulmonary hypertension.[2 5] Infusion of live group B β haemolytic streptococcus, streptococcal toxin, or purified *Escherichia coli* endotoxin in animal models causes pulmonary hypertension, which is associated with high plasma thromboxane B_2 concentrations.[5] It has also been suggested that pulmonary hypertension seen in perinatal aspiration syndrome is mediated by release of platelet thromboxane A_2 in the lungs.[2] Inhaled amniotic fluid may be absorbed by the lungs and cause local platelet aggregation. Thromboxane A_2 is then released from the platelets and causes pulmonary vasoconstriction.[2]

Our results suggest that production of platelet thromboxane A_2 is decreased in persistent pulmonary hypertension of the newborn. The lowest values were found in cases of severe meconium aspiration syndrome, but no correlations between the simultaneous blood gas values and production of platelet thromboxane B_2 were found. Although samples in the two groups were drawn from different sites, this should not influence the thromboxane B_2 results because they were expressed as nanograms per number of platelets. The high plasma thromboxane B_2 concentration in previous studies[5 6] may originate either from the lungs or from hyper-reactive platelets, which release thromboxane B_2 excessively in vivo. If this in vivo stimulation of the release of thromboxane B_2 lasts long enough it may lead to exhaustion of the capacity of the platelets to produce thromboxane B_2. The present in vitro data on reduced production of platelet thromboxane B_2 may support this hypothesis.

Vasoactive prostanoids and their inhibitors may be useful in the treatment of some forms of pulmonary hypertension. Selective inhibition of thromboxane A_2 formation is effective in some examples of experimental pulmonary hypertension.[5] The biological antagonist of thromboxane A_2, prostacyclin, has been successfully used to reduce pulmonary hypertension [6] The response to this treatment with dilator could be enhanced if the platelet formation of the vasoconstrictive thromboxane A_2 is already diminished, as in the present cases.

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Noonan's syndrome and neurofibromatosis

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SUMMARY A child with Noonan syndrome and multiple cafe au lait spots, compatible in size and number with von Recklinghausen's neurofibromatosis, is presented. These features may represent a distinct genetic entity rather than the coincidence of two diseases.

Von Recklinghausen's neurofibromatosis and Noonan's syndrome share several similar clinical findings, such as short stature, mental retardation, pubertal changes, kyphoscoliosis, and right sided congenital heart disease.[1 2] Multiple cafe au lait spots are regarded as pathognomonic of von Recklinghausen's neurofibromatosis[3] and have not been reported with Noonan's syndrome.[2] A few children have been reported recently with typical features of Noonan's syndrome and multiple cafe au lait spots and were diagnosed as neurofibromatosis-Noonan's syndrome.[4–6] We present one more case of this latter syndrome. Such cases have not been reported previously in paediatric publications.

Case report

The patient was referred to our clinic at the age of 12 years because of severe headaches. He was the fourth son of unrelated parents of Moroccan origin, both aged 47 years. The parents and the three siblings were all healthy, having normal height and weight and unremarkable physical findings. Pregnancy and delivery had been normal and birth weight had been 3500 g. Multiple cafe au lait spots were noted at birth and later were found to have increased in size and number. He sat up at the age of 9 months and walked alone at 18 months. No developmental problems were noted until he was of school age, when severe learning difficulties became apparent.

On examination, his weight was 30 kg (12th centile), height 132 cm (<3rd centile), and head circumference 55·5 cm (75th centile). There was bilateral ptosis of the eyelids, with a downward palpebral slant and low set ears (Figure (a)). The palate was high arched and the teeth overcrowded. His hair was coarse with a low posterior hairline. The neck was short with prominent pterygium colli. He also had pectus excavatum and cubitus valgus. Physical examination of the heart yielded normal results. The testicles were in the scrotum, with a volume of 2 ml. No pubic or axillary hair was present. Scattered over the entire skin surface were more than 20 cafe au lait spots (Figure (b)), with a diameter ranging from several millimetres to 10 cm. Of these, 10 were more than 1·5 cm in diameter. No fibromata could be found. Electrocardiography and echocardiography yielded normal results. Roentgenographic survey of the skeleton failed to show any bone anomaly aside from the pectus excavatum and cubitus valgus. His bone age was 7 years. The karyotype was normal. Computed tomography of the brain, performed because of the severe headaches, did not show any disease.

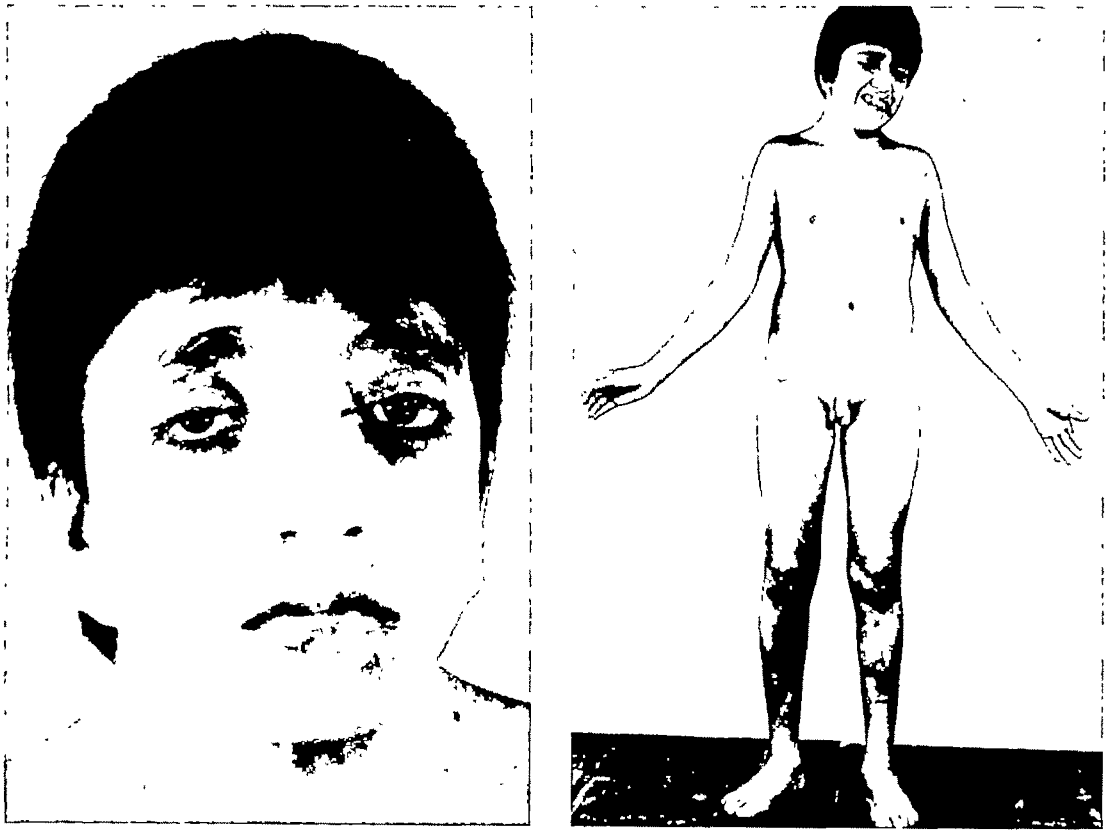

Figure (a) *Frontal face photograph of the child (left),* (b) *general appearance of the child (right)*

Discussion

The present case shows some of the classical features of Noonan's syndrome—that is, short stature, pterygium colli, low set ears, ptosis, pectus excavatum, kyphoscoliosis, cubitus valgus, intellectual impairment, and delayed puberty.[2] The syndrome is delineated principally at the clinical level and the combination of features suggests the diagnosis. Nevertheless, the findings of numerous cafe au lait spots in appropriate size and number established the diagnosis of von Recklinghausen's neurofibromatosis. The coexistence of both syndromes in one patient confirmed the diagnosis of neurofibromatosis-Noonan's syndrome.[4-6]

The term neurofibromatosis-Noonan's syndrome was coined in 1985 by Opitz *et al*, who suggested the syndrome to be a nosologically discrete, real biological entity of unknown aetiology.[4] Although they believed neurofibromatosis-Noonan's syndrome to be fairly common,[4] only a few such patients have been reported, and those reported had multiple cafe au lait spots and a phenotypic appearance appropriate for Noonan's syndrome. They seemed to have few or no Lisch nodules. Boys were more likely to have fusiform swelling of nerve strands, while girls tended to show the classical cutaneous neurofibromata. The reported cases as well as that reported by us may point toward two additional important diagnostic findings. The patients reported so far have been single cases with no familial incidence. It seems that the incidence of cardiac anomalies in these patients is low. In only one patient was there an appreciable systolic murmur; the echocardiogram, however, yielded normal results in this patient.

The aetiology of neurofibromatosis-Noonan's syndrome is not known. The possibility that both Noonan's syndrome and von Recklinghausen's neurofibromatosis occurred coincidentally in one patient is real, but most likely has a very low incidence. On the other hand, it may be suggested that these cases represent a separate genetic condition caused by a mutation at a locus that is different from either the neurofibromatosis or the Noonan's syndrome loci; alternatively, the Noonan's syndrome and neurofibromatosis loci may be close together on the same chromosome and the neurofibromatosis-Noonan's syndrome may be caused by a simultaneous mutation at both loci (probably a submicroscopic chromosome deletion). It seems that more reports of such patients are needed to learn the full extent of the clinical presentation of neurofibromatosis-Noonan's syndrome.

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Hydrops fetalis due to abnormal lymphatics

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SUMMARY A case of generalised lymphatic abnormality that presented with hydrops fetalis is described. This seems to be the first such case reported

The reported incidence of non-immunological hydrops fetalis varies from one in 1400[1] to one in 7143.[2] Causes are identified in 56%[3] to 85%[1] of cases, among which cardiac arrhythmia, thalassaemia, twin to twin transfusion, and congenital heart disease account for half.[3] Localised lymphatic abnormalities—that is, cystic hygroma, pulmonary lymphangectasia,[2 4] and prolonged chylous ascites[2]—may be causes, but there are no reports of generalised lymphatic abnormalities being associated with hydrops.

Case report

The parents were unrelated members of a vagrant family. The mother was a heavy smoker (40 a day) and had attended antenatal clinic only once, at which time polyhydramnios was noted. At 34 weeks she went into spontaneous labour and a hydropic, female infant weighing 3410 g with a grossly oedematous placenta was delivered vaginally. The child required immediate intubation and ventilation but did not appear pale, and auscultation of the praecordium was normal with no tachycardia.

The mother's blood group was A Rh-positive and the baby's O Rh-positive with a negative direct Coombs test. The baby's haemoglobin concentration was 14·9 g/dl, total white blood cell count $16{\cdot}6\times10^9$/l, and platelets 202×10^9/l, with a normal film. Biochemical values were normal except for an albumin concentration of 22 g/l (normal 35–50 g/l), plasma osmolality 268 mOsm/kg (normal 289–308 mOsm/kg), and IgG 4·9 g/l (normal 7–19 g/l). There was no proteinuria. Subsequently, the chromosomes were found to be normal, and there was no serological evidence of congenital infection. A chest radiograph showed a normal heart and small pleural effusions. The electrocardiogram yielded normal results and echocardiography showed a structurally normal heart with mild ventricular dysfunction.

Treatment was started with digoxin, diuretics, and salt poor albumin. By day 3 her bilirubin concentration had reached 300 µmol/l (normal 1–17 µmol/l) and a two volume exchange transfusion was performed. On day 5 her urine output decreased, her plasma urea rose to 22 mmol/l (normal 2·5–8·0 mmol/l), and peritoneal dialysis was started. The plasma albumin concentration was 26 g/l but her oedema did not improve and a sample of lower limb tissue fluid had an albumin concentration of 19 g/l. Her haemoglobin concentration fell to 5·9 g/dl with no evidence of haemolysis or haemorrhage, but she did develop a generalised, blue skin discoloration.

The oedema slowly decreased, revealing small blue variceal vessels in both groins, and it became possible to insert a left internal jugular venous line and remove her umbilical lines. A sample taken from this line had a haemoglobin concentration of 3 g/dl. Clinically, this was very unlikely and samples were taken from the groin vessels and a scalp vein, which showed haemoglobin concentrations of 1·7 and 12·9 g/dl, respectively. These bizarre results suggested an anomaly of venous development and contrast studies were performed.

Niopam was injected into the left inguinal region and delineated a group of large vessels (Fig. 1). Contrast spread down the left leg and then across the lower abdomen filling smaller, superficial vessels. Large, deep vessels were then outlined in the right leg and finally the contrast spread up the right abdominal wall and stopped in blind ending vessels in the right axilla. Figure 2 shows the spread of contrast from the 'internal jugular line', delineating a large vessel in the middle, which disappears at the level of the fourth lumbar vertebra.

^{99m}Tc labelled red cells were injected into the scalp vein and after two hours a normal blood pool was seen. By 12 hours there was excessive activity in the lower half of the body, suggesting abnormal accumulation of cells. Counts on the fluid from the groin vessels were initially high and fell gradually over 24 hours. These results suggested a major degree of communication between the abnormal vessels and the venous system.

By 3 weeks of age her albumin concentration was 40 g/l and she had improved markedly with only

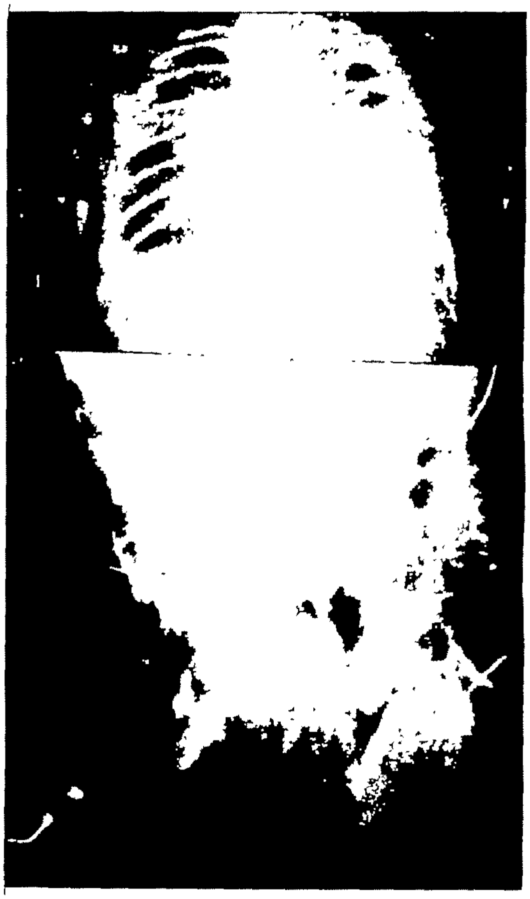

Fig. 1 *Contrast injection into left groin, showing abnormal vessels ending blindly by the right axilla (Composite figure from two radiographs)*

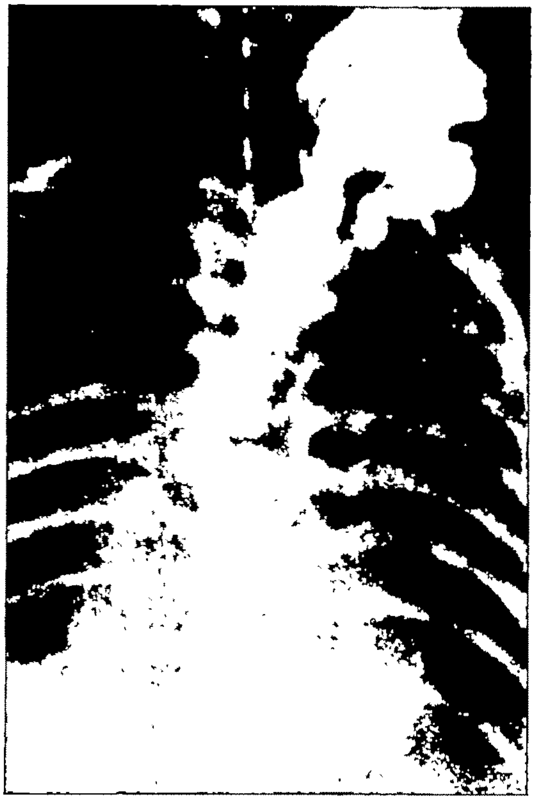

Fig 2 *Contrast injection into left 'internal jugular line'*

slight limb oedema remaining. Mechanical ventilation was stopped, oral feeding started, and she was discharged One month later her generalised oedema recurred and she developed pneumonia and required mechanical ventilation Chylous fluid was obtained from the subcutaneous tissues of all four limbs and the pleural spaces. Her plasma albumin concentration was 26 g/l Renal failure developed and she died aged 66 days. Permission for a postmortem examination was refused.

Discussion

The radiological appearance of these vessels was neither typically lymphatic nor venous and probably reflected a shared developmental failure of the two systems. When enterally fed the child had an abnormal accumulation of chyle in the limbs and body cavities. It would therefore seem reasonable to classify this abnormality as a primary lymphatic deformity of mixed vascular type with abnormal chylous flow.[5]

Conventionally, the causes of hydropic oedema are described as anaemia, heart failure, and hypoproteinaemia or low colloid osmotic pressure Barnes, however, pointed out that these conditions can exist in extreme forms without causing oedema and that therefore the mechanisms are more complex.[6]

In this case we found an extremely high concentration of albumin in the extracellular fluid and it was only when the plasma albumin had risen to 40 g/l that the baby's generalised oedema improved. As a result of the abnormal chylous flow, however, the child could not maintain its intravascular albumin when enterally fed and was re-admitted with a recurrence of generalised oedema. It seems likely, therefore, that the disturbed balance between intravascular and extravascular albumin due to the hybrid nature of the lymphatic and venous systems played an important part in the original hydropic appearance, independently of simple, mechanical lymphatic obstruction

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Prognosis of chronic hepatitis B transmitted from HBsAg positive mothers

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SUMMARY Nine children born to HBsAg positive mothers, who became chronic HBsAg carriers with associated liver disease, were followed for five to 10 years. Five children with active hepatitis or active cirrhosis at presentation achieved complete remission within six years, while three HBeAg positive patients with minimal histological lesions remained unchanged.

A number of studies performed in the last decade have emphasised the role of perinatal transmission in the spread of hepatitis B virus (HBV) infection in endemic areas.[1] Indeed, children infected in the perinatal period by their mother positive for hepatitis B surface antigen (HBsAg) often become chronic HBsAg carriers with or without associated liver disease. Up to date, however, few studies have examined the long term outcome of HBV infection and disease acquired early in life.[2]

We report the natural history of chronic hepatitis B in nine children born to HBsAg positive mothers during a follow up of five to 10 years.

Patients and methods

The nine infants included in the study (five boys and four girls) were born to mothers known to be HBsAg positive at the time of delivery and had acquired HBV infection in the perinatal period.

The clinical and HBV state of the nine mothers at delivery is shown in the Figure. Three of them (cases 7, 8, and 9) had developed symptoms or signs of acute hepatitis B at the time of delivery or a few days later. Retrospective testing of serum samples revealed a transient hepatitis e antigen (HBeAg) positivity in all three cases, which subsequently resolved. Two mothers (cases 5 and 6) had biochemical features of liver damage associated with HBsAg positivity: retrospective testing revealed HBeAg positivity in both cases, while a liver biopsy examination performed a few months after delivery was consistent with chronic active hepatitis in both cases. The remaining four mothers (cases 1–4) were asymptomatic HBsAg carriers with normal transaminase activities. Testing for HBeAg and antibodies to HBeAg was not performed at delivery, but results obtained at the time when the children presented to us showed anti-HBe positivity in serum in all cases.

For different reasons none of the nine children received specific immunoglobulin at birth. HBV vaccine was not yet available when the children acquired the infection. During the perinatal period none of the other household contacts of these patients was found to be HBsAg positive.

Three infants (cases 1, 2, and 5 in the Figure) presented to us at 3 months of age with symptoms or signs (jaundice (1 case), anorexia, vomiting, and hepatomegaly) of liver disease Peak alanine aminotransferase (ALT) activities, ranging between 350 (in the jaundiced patient) and 1600 IU/l (normal

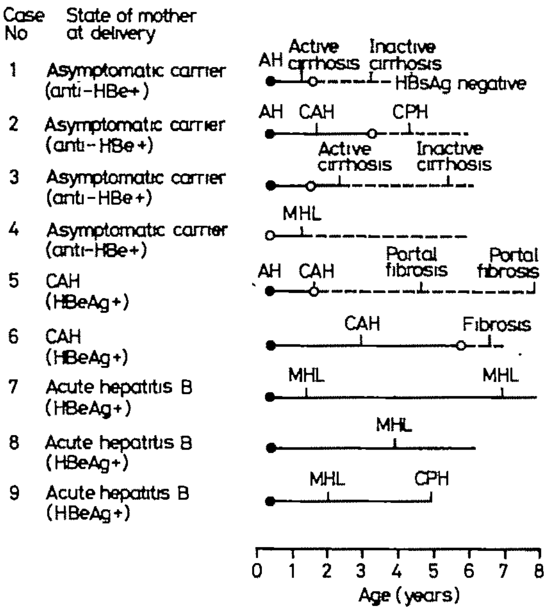

Figure *State of the mother at delivery and features of liver disease during follow up in nine children born to HBsAg positive mothers ●=HBeAg positive, ○=anti-HBe positive, ——=abnormal alanine aminotransferase, – – –=normal alanine aminotransferase, AH=acute hepatitis; CAH=chronic active hepatitis, CPH=chronic persistent hepatitis; MHL=minimal histological lesions* values <50 IU/l) were consistent with acute hepatitis. In all three cases symptoms subsided spontaneously within eight weeks. The remaining six children were asymptomatic and were found to be HBsAg positive with abnormal transaminase activities (ALT range 60 to 150 IU/l) at the age of 3–4 months when routine tests were performed due to the HBsAg carrier state of their mother Antibody to hepatitis delta antigen was negative in all cases. Six months after the onset of infection all nine children were still HBsAg positive and were therefore considered to be chronic HBsAg carriers. They have been followed up in the outpatient clinic and tested for ALT and HBV markers every four to six months. One or more liver biopsy examinations have been performed by the Menghini technique in each patient during observation.

Methods. HBsAg, HBeAg, and anti-HBe, as well as anti-delta antibody in serum, were detected by commercial radioimmunoassay techniques (Abbott Laboratories, Chicago, Illinois).

Results

All children were completely asymptomatic six months after the onset of infection and continued to be asymptomatic throughout the observation period of five to 10 years (mean (SD) 6·5 (1·0) years). Hepatomegaly was present in six cases and splenomegaly in two. None of the patients received treatment.

As shown in the Figure, three of four children born to asymptomatic anti-HBe positive mothers (cases 1, 2, and 3) were HBeAg positive and developed features of chronic active hepatitis, with associated cirrhosis in two cases. Seroconversion from HBeAg to anti-HBe with subsequent sustained normalisation of enzymes occurred in all three children within the third year of life. A liver biopsy taken one to three years after seroconversion showed disappearance of histological activity in all three cases A boy with inactive cirrhosis cleared HBsAg from serum at the age of 3 years

The fourth patient born to a anti-HBe positive mother (case 4), who was already anti-HBe positive at first testing, showed minimal histological lesions on biopsy examination (minimal lymphocellular infiltrate and mild fibrosis of the portal triad) and normalised ALT activities during the second year of life. Both children born to HBeAg positive mothers with chronic active hepatitis (cases 5 and 6) developed HBeAg positive chronic active hepatitis. They seroconverted to anti-HBe with subsequent remission of the disease at 18 months and 6 years of age, respectively. A liver biopsy taken after anti-HBe seroconversion was consistent with portal fibrosis in both cases.

Finally, all three children born to mothers with acute hepatitis at delivery (cases 7, 8, and 9) developed non-progressive liver disease. During the whole follow up they remained HBeAg positive with minor ALT fluctuations. During follow up none of the patients developed features of liver failure or clinical signs of portal hypertension.

Discussion

In this small series maternally transmitted HBV infection resulted in a chronic HBsAg carrier state associated with a variety of clinical and histological patterns, ranging from minimal liver lesions to cirrhosis. These patterns seemed to be related to the clinical and virological state of the mother at delivery. Indeed, all three children born to mothers with acute hepatitis B became asymptomatic HBeAg positive carriers with minor liver lesions, according to the observations of Schweitzer *et al*,[3] while children born to HBeAg positive mothers with chronic active hepatitis themselves developed an active liver disease. Two different patterns were observed instead in the offspring of asymptomatic anti-HBe positive mothers: a mild liver damage associated with anti-HBe positivity or a severe liver disease, sometimes presenting as acute hepatitis and progressing to early cirrhosis.

It has been hypothesised that maternally transmitted virus charge may influence the degree of specific immune response in the infected baby.[4] According to this hypothesis we could suggest that in our patients a heavy virus charge, capable of inducing immune tolerance, had been transmitted by mothers with acute hepatitis at delivery, while a lower charge, inducing an efficient, although inadequate, immune response to the infected hepatocytes, had been transmitted not only by anti-HBe positive mothers but also by HBeAg positive mothers with chronic active hepatitis.

The outcome of liver disease in our patients was closely related to the severity of liver lesions and to HBeAg/anti-HBe state at presentation, as also suggested by previous observations in children with chronic type B hepatitis.[5] In fact, remission of liver disease was observed not only in the child with minimal histological lesions associated with anti-HBe positivity but also in children with chronic active hepatitis or active cirrhosis after anti-HBe seroconversion. Conversely, all three children with minimal histological lesions and HBeAg positivity at presentation remained unchanged throughout the observation period, as also described by Tong *et al* in some of their cases.[2]

According to recent epidemiological observations[6] all our patients, who became chronic HBsAg carriers early in life, may develop hepatocellular carcinoma: continuing surveillance, however, will clarify whether the different histological and virological patterns observed in these children during the early phase of HBV infection may influence the final outcome of their liver disease.

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Personal practice

Antibiotic use in the neonatal unit

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The changing pattern of organisms causing neonatal sepsis, from *Streptococcus pyogenes* in the 1930s to *Staphylococcus aureus* in the 1950s and more recently to Gram negative bacilli and the group B streptococcus,[1] has been reflected in the development of new antibiotics. In particular semi-synthetic penicillins and the so called third generation cephalosporins have been introduced. both with activity against a wide range of Gram negative as well as some Gram positive organisms.

There remains some uncertainty about whether it is best to use these antibiotics for all episodes of suspected sepsis or to reserve them for episodes not responding to more conventional antibiotics. In a recent survey of antibiotic use in neonatal units in the United Kingdom and Eire, conducted through the British Association of Perinatal Paediatrics, replies were received from 30 institutions, who regularly used 24 different antibiotic policies. This may reflect a rational approach to changing causes of sepsis and changing antibiotic resistance patterns but may equally be due to uncertainty over which of the many possible antibiotics to use.

The aim of this article is to review antibiotic options in the light of known causes of neonatal sepsis and our experience and to give a rational explanation of our own antibiotic policies.

Early onset sepsis

Most neonatal units use different antibiotics for babies with onset of sepsis within the first 48 hours of life (early onset) and those with sepsis starting after 48 hours (late onset). Early onset sepsis is almost invariably due to organisms acquired transplacentally or to ascending infection from the vaginal canal, whereas onset after 48 hours may be due to organisms acquired either at delivery or on the neonatal unit.[1]

Early onset sepsis is usually treated with penicillin or ampicillin and an aminoglycoside, as group B streptococcal infection and infection with Gram negative organisms are currently the most commonly identified causes.[1] Babies with early onset sepsis may present with non-specific signs or may have a respiratory illness that, in the case of group B streptococcal infection, is clinically and radiologically indistinguishable from hyaline membrane disease.[2] In Britain the incidence of early onset group B streptococcal sepsis is about 0·3 cases per 1000 live births,[3] considerably lower than in the United States where it is 2·0–3·7 per 1000.[2] It may rise sporadically to higher rates in some areas, and an incidence of 1·4 per 1000 was described in West Berkshire in 1978.[4] The low incidence of group B streptococcal sepsis has meant that short term studies of the newer ureidopenicillins[5] or third generation cephalosporins[6 7] in the management of early onset sepsis have included very few cases of group B streptococcal disease. Thus the studies have been too small to show any difference between the newer antibiotics and penicillin, which is the treatment of choice for group B streptococcal sepsis.[2]

The main reasons proposed for researching alternative treatments to penicillin and an aminoglycoside are the potential ototoxicity and nephrotoxicity of aminoglycosides and the cost of monitoring blood concentrations. There is no evidence that aminoglycosides cause appreciable toxicity in neonates [8 9] We measure serum gentamicin concentrations after 48 hours when a steady state has been reached,[9] and a decision is then made whether or not to stop antibiotics This ensures early review of the necessity for antibiotics, often eliminates the expense of measuring concentrations, and minimises the risk of toxicity.

In the 18 months from 1 May 1984 to 31 October 1985 we have diagnosed 18 episodes of early onset sepsis In this time there were 8708 live births at the hospital. There have been six cases of group B streptococcal sepsis, with four deaths. In addition, although not fulfilling our strict criteria of sepsis as positive blood or cerebrospinal fluid cultures, or both, two babies heavily colonised with group B streptococci but with negative blood cultures died from histologically proven pneumonia. Our current policy is high dose penicillin (100 000 units/dose/kg every 12 hours) and gentamicin (2·5 mg/kg/dose intramuscularly every 12 hours for babies with birth weight over 1500 g, every 18 hours if under 1500 g) for suspected early onset sepsis. As group B streptococcal infection was the only detected infectious cause of early onset mortality it would be illogical for us to use any alternative to penicillin or ampicillin for the treatment of early onset sepsis. The fact that 50% or more of babies with early onset group B streptococcal sepsis still die despite early treatment with penicillin[2] suggests that alternative treatment strategies are needed. Boyer *et al* in Chicago have shown that among pregnant women colonised with group B streptococcus a group can be identified with preterm labour, rupture of membranes for greater than 18 hours, or maternal fever, whose infants comprise three quarters of all cases of early onset sepsis.[10] Their recent study shows that the incidence of early onset group B streptococcus sepsis can be significantly reduced by giving the at risk mothers ampicillin during labour.[11]

Some authors have advocated administration of a single dose of intramuscular penicillin to all newborns as prophylaxis against group B streptococcal infection. One group found that this significantly reduced colonisation and sepsis, but the slight improvement in mortality from organisms sensitive to penicillin compared with the control group was offset by a rise in mortality from organisms resistant to penicillin.[12 13] In a separate study of high risk babies under 2000 g, single dose penicillin prophylaxis did not alter the incidence of, nor mortality from, group B streptococcal sepsis[14] It may be possible to identify term babies on the postnatal wards with group B streptococcal pneumonia by measuring their respiratory rate; a non-invasive method has been described.[15]

Ampicillin is widely used in the USA as an alternative to penicillin and is active against some of the Gram negative organisms causing early onset sepsis. It is possible, however, that the use of broad range antibiotics such as ampicillin and the third generation cephalosporins may be a factor in promoting systemic candidiasis and that use of ampicillin may encourage plasmid mediated multiple drug resistance. We feel justified in using the narrower range penicillin G in view of the lack of morbidity caused by organisms other than group B streptococci.

Late onset sepsis

Gram negative organisms are far more likely to cause late onset than early onset sepsis. and this has been the rationale for some units changing to third generation cephalosporins for the treatment of suspected late onset sepsis.[6 7] In particular *Pseudomonas aeruginosa*, which was reported by seven of the 30 British institutions to colonise many of their patients, has caused problems in many European countries, and the high activity of ceftazidime against *Pseudomonas* is attractive.

The initial treatment for late onset sepsis, excluding meningitis, in Oxford is flucloxacillin and gentamicin. The original basis for the use of flucloxacillin was the high incidence of infections with *Staph. aureus* in the 1960s. Although *Staph. aureus* is now an uncommon cause of late onset sepsis, many units have reported *Staph. epidermidis* to be their commonest cause of late onset septicaemia,[16] even allowing for difficulty in interpreting the significance of blood cultures positive for what is also a common skin contaminant. In fact neither *Staph. aureus* nor *Staph. epidermidis* are common causes of late onset sepsis in Oxford (Table) A possible reason is that enteral feeds are begun very early in this unit and central venous catheters are rarely used, *Staph. epidermidis* being notorious for colonising venous catheters and other indwelling synthetic materials

Twenty seven episodes of late onset sepsis occurred in 18 months in Oxford, nine being polymicrobial (Table). Gram negative organisms predominated, but faecal streptococci comprised the commonest single organism. The third generation cephalosporins are inactive against enterococci,[17] and colonisation with faecal streptococci is common when these antibiotics are widely used.[7] We would substitute a third generation cephalosporin for flucloxacillin if blood cultures were growing Gram negative bacilli and the patient was still unwell on flucloxacillin and gentamicin, this happened in six of the 27 episodes of septicaemia We would not use third generation cephalosporins as first line treat-

Table *Bacterial isolates in 27 episodes of septicaemia (nine polymicrobial) after 48 hours of age in the Neonatal Unit, John Radcliffe Hospital, Oxford, between 1 May 1984 and 31 October 1985*

Organism	*No*
Faecal streptococci	11
Pseudomonas	9
Klebsiella	5
Escherichia coli.	3
Staphylococcus epidermidis	3
Serratia	2
Clostridium	1
Acinetobacter	1
Achromobacter	1
Total	36

ment for suspected sepsis because of the high incidence of infection with faecal streptococci.

There were two deaths among the babies with late onset sepsis One baby with *P aeruginosa* meningitis and septicaemia died after treatment for 24 hours despite receiving ceftazidime and netilmicin from the time of diagnosis, while a preterm baby with cystic fibrosis and recurrent pneumonias not responding to treatment developed septicaemia with *P. aeruginosa* and *Str. faecalis* as a terminal event.

All other babies recovered. Colonisation of infants with aminoglycoside resistant strains was common. Up to 25% of *Pseudomonas* and up to 50% of coliforms were resistant to the aminoglycoside in use, but these strains rarely caused sepsis. Only two of the bacteria isolated from babies with septicaemia, a *P. aeruginosa* and an *Achromobacter xylosoxidans,* were resistant to aminoglycosides and one baby had a shunt infection with *P. aeruginosa* resistant to ceftazidime and piperacillin but not aminoglycosides. All three babies recovered Other workers have found a similar lack of correlation between colonisation with resistant organisms and episodes of systemic sepsis.[18] Our low mortality and morbidity from late onset sepsis do not warrant any change from our present policy of flucloxacillin and gentamicin for suspected sepsis after 48 hours of age. Continued surveillance of the outcome of late onset infections will determine the effectiveness of this approach. We reserve the use of third generation cephalosporins for severe Gram negative infections not responding to conventional treatment, with the aim of limiting the emergence of strains resistant to these important antibiotics.

Late onset pneumonia

Babies receiving artificial ventilation will often have episodes of increased pulmonary shadowing on *x* ray film, which could be due to infection or pulmonary oedema, and the distinction is often extremely difficult. When the shadowing resolves within 24 hours fluid seems the likely cause. Often, however, the diagnosis is unclear and empirical treatment with antibiotics is necessary. We base this treatment on the results of thrice weekly cultures of endotracheal secretions from artificially ventilated babies and would only treat if there were *x* ray changes and clinical deterioration. Some neonatal units treat endotracheal cultures regardless of the clinical picture or *x* ray appearance. As about 50% of our babies develop endotracheal tube colonisation with a potential pathogen that is not eradicated by antibiotics this practice will result in considerable overuse of antibiotics.

Duration of treatment

Altogether, 96% of blood cultures that grow an organism do so within 48 hours and 98% within 72 hours.[19] Babies treated with antibiotics for over 72 hours are more likely to become colonised with Gram negative organisms.[20] Furthermore, the old idea that courses of antibiotics should be completed to prevent the emergence of resistant strains has been superseded by the realisation that increasing use of antibiotics selects for antibiotic resistant strains.[21] We, therefore, stop antibiotics given for suspected early or late onset sepsis after 48 to 72 hours if blood cultures yield negative results. When pneumonia seems a strong likelihood but the results of blood cultures are negative we would usually give five days of antibiotics, but this duration of treatment is purely empirical and physiotherapy seems at least as important as antibiotics. Proven septicaemia is treated for at least 10 days and there have been no recurrences.

Surveillance

Unlike other workers[22] we have not found that nasopharyngeal colonisation with a pathogen is a common antecedent of late onset septicaemia with the same organism. On the contrary, of the 26 episodes of late onset septicaemia in which the nasopharyngeal and surface colonisation of the baby was known, the bacteria isolated from blood cultures were only colonising the baby in 10 cases. Furthermore, although the results of endotracheal and surface cultures showed that resistance to aminoglycosides in colonising organisms was common, this was not reflected in episodes of sepsis with resistant organisms. Thus routine surveillance of surface or stool bacteria is not performed on our unit. We do, as stated previously, routinely culture endotracheal secretions as this often affects choice of treatment with antibiotics for pneumonia.

Bacterial meningitis

The treatment of proven or suspected bacterial meningitis will depend on the Gram's stain of the cerebrospinal fluid (CSF) In the absence of a shunt or of signs of disseminated staphylococcal sepsis, Gram positive cocci in the CSF will almost certainly be group B streptococci. The treatment for group B streptococcal meningitis is high dose penicillin G (150 000 to 250 000 units/kg/day) with or without gentamicin.[23]

When Gram negative bacilli are seen in the CSF the optimum treatment is less clear cut. Most units in the United Kingdom still use chloramphenicol (de

Louvois J Personal communication), but results with this drug have not been impressive[24 25] and its toxicity has been a major problem.[26] Furthermore, *Pseudomonas* and many coliforms are fairly resistant to chloramphenicol.[25] The third generation cephalosporins have excited attention because of their excellent penetration of CSF and high activity against Gram negative organisms, although only ceftazidime is potent against *Pseudomonas*. Experience with these drugs, however, is very limited. Drug resistant strains may emerge during treatment.[27] Although bacteria are rapidly eliminated from the CSF, there is a worry that the rapid acquisition of high CSF cidal concentrations might itself be deleterious, in that rapid killing of large numbers of Gram negative organisms could cause massive release of endotoxin [28] Previous attempts, by the Neonatal Meningitis Cooperative Study Group in the USA, to improve the delivery of antibiotics to the meninges and ventricles of neonates and infants with Gram negative enteric meningitis by the use of intrathecal[29] and intraventricular[30] administration of aminoglycosides have not improved outcome. But perhaps the most important finding in these studies was the low mortality and morbidity in the control group: babies who were treated with parenteral ampicillin and gentamicin alone. In the former study the mortality of the control group was 32%,[29] and in the intraventricular study was 12·5%, while eight of the 21 survivors were normal and eight had mild to moderate disability.[30] This was despite 46% of strains being resistant to ampicillin. The current multi-centre study from the same group is comparing moxalactam with ampicillin and gentamicin for the treatment of Gram negative meningitis Until the results of this study are known, parenteral ampicillin and gentamicin is our treatment of choice for Gram negative meningitis. The use of third generation cephalosporins is understandable; use of the combination of chloramphenicol and a third generation cephalosporin is contraindicated because these drugs are antagonistic.

In roughly 20% of cases of bacterial meningitis the initial CSF Gram stain will not reveal organisms. In addition, neonates have often had intraventricular haemorrhages and when the red cells have degenerated the CSF white cell count can be artificially high. Thus it is not uncommon to have to prescribe 'blind' treatment for possible neonatal meningitis Ampicillin and gentamicin, for the reasons outlined above, will be appropriate for Gram negative bacilli. They are also excellent treatment for group B streptococcal and listeria meningitis and toxicity is low. Alternative treatments sometimes used for suspected bacterial meningitis with no organisms are chloramphenicol, with its risk of toxicity, and the third generation cephalosporins, whose activity against listeria and group B streptococci are in doubt.

Conclusion

The emergence of resistant bacteria, a high rate of bacterial infections in neonates, and the poor outcome of some of these infections mean that the antibiotics used in neonatal units need frequent scrutiny. Use of antibiotics should, however, be based on actual episodes of sepsis rather than patterns of colonisation and on the outcome of those episodes of proven sepsis. The temptation to use new antibiotics extensively should whenever possible await controlled studies of their efficacy that show their superiority to existing regimens. In the absence of such studies it might be sensible to restrict their use to babies not responding to conventional treatment.

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Archives of Disease in Childhood, 1987, **62,** 209–211

Personal view

Epilepsy and prejudice

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> "It is not good to have respect of persons in judgment." Proverbs xxiv, 23.

In his massive study of social behaviour, 'Social being', the philosopher and social psychologist Rom Harré declares, in a throwaway line, that the whole of man's social behaviour is directed at the maintenance and management of his self esteem.[1] Social life, according to Goffman,[2] can be seen as a series of negotiations in which the self is presented to its best advantage, despite its many defects, to secure and maintain the best possible level of social support. Social support in its turn is crucial to the maintenance of health. Totman summarised work that shows how being separated from one's appropriate social reference group and being required to learn new sets of social rules lead to ill health.[3] Prejudice is a social Exocet missile, a long range destroyer of esteem. Without reference to the quality of local social skirmishes, prejudice annihilates one particular group of protagonists.

Prejudice has changed from meaning either a prejudgment or one made on the basis of inadequate evidence.[4] It now means ascribing to another person or group attributes of such overwhelming importance that they override their individual characteristics.[5] The validity, the 'truth', of the discriminating characteristic is irrelevant and the precise characteristics of the outgroup may be quite hard to identify at times. It is enough to be 'not us'. 'The mere fact of division into groups' wrote Tajfel 'is enough to trigger discriminatory behaviour' [6] Thus posing the question 'Are the more stupid people sitting on the right side of this room?' to an audience creates a climate in which it becomes necessary to know from whose perspective the room is to be viewed rather than one that rejects a nonsensical, ridiculous question. It is the possibility of producing such spurious and divisive questions that has led to anxiety about 'labelling' in medicine, especially in the psychological and social aspects of medicine.

Tajfel's hypothesis that divisiveness inheres in categorisation was shown in experiments with perfectly normal secondary school children. An entirely spurious but apparently normal physiological difference was the basis of their grouping. In subsequent scoring tasks the children allocated marks, worth money, differentially dependent upon whether the recipient was or was not a member of the same ludicrous 'grouping' as the scorer.[6] Since, as will be argued, categorisation and labelling are also absolutely necessary to thinking,[7] it is clear that a conscious effort has to be made to keep labels uncorrupted as far as possible. But labels like 'epileptic' are handed on encrusted with the accretion of ages. Many of the papers written about epilepsy and prejudice imply that the prejudice against epileptics is wrongly conceived, ignorant, or irrational and that if more people realised that people with epilepsy were not necessarily mentally retarded or insane matters would improve. Irrationality is not the basis for my regarding negative views about people with epilepsy as prejudiced, in the same way that I would not regard proving myself non-Jewish an appropriate defence against anti-Semitism.

Prejudice is not an attribute of some rather nasty people out there in the world. It is a universal characteristic originating in the categorising process that underpins thinking. Labels are discriminatory, as Tajfel found, because that is the purpose of labels. It follows that there must be positive as well as negative prejudice. Doctors benefit from being accorded attributes that they might not have (such as a doctorate!) and so are certain treatments and medicines (the placebo response). More important is to consider what causes certain phenomena to be attributed negative and others positive characteristics Why would epilepsy be so pervasively negatively regarded?

The moral and ethical problems and some of the characteristics of stigma are revealed in the case of Sharon.

> Sharon was aged 15 when she was referred to us because it was thought unlikely that her attacks were epileptic and because of her disagreeable behaviour. She came from a chaotic and angry family in which her temper tantrums, her 'fits of temper', had been a lifelong method of coping. In recent months she had been 'found on the floor in a pub' where, in fact, she had been drinking and where, on another occasion, she had 'laughed herself to the floor'. In explaining her absence from school to the school doctor, mention of these attacks led to detailed enquiries about their possible nature. Auras were enquired into and auras of taste and smell were agreed to. A neurological opinion was sought, an electroencephalogram 'focus' appeared, and phenytoin was prescribed. The tablets were promptly used in a suicidal gesture. The family ignored the gesture but the girl told the neurologist that she thought she was going mad. It was not possible to discover any unequivocal evidence of epilepsy.

Is it more prejudicial to call this girl epileptic than not to do so? Is there any need for any one component of her sickness to be explained by another? As I see it, the moral aspects of sickness are forced forward into prominence as the 'disease' component recedes[8] and in a chronic, sporadic, arcane disorder moral concerns can come to dominate the whole management. Prejudicial responses in health care professionals may determine very important aspects of policy in such cases.

In his chapter in 'Introduction à la psychologie sociale' Tajfel writes, 'In the case of strong negative evaluation of a category it is very important that an individual who is a member of it should not be 'missed', with the attendant danger of his assignment, by mistake, to a positive valued category . . . errors of assignment in a negative valued category will be in the direction of overinclusion.'[9] Think of what constituted 'a communist' under McCarthyism. Sharon *might* be an epileptic. Woodland fungi 'might' be poisonous so they are left alone on the whole.

Sharon's predicament becomes like that of the child accused of sorcery reported by Levi Strauss.[10] 'How can an innocent person accused of sorcery prove his innocence if the accusation is unanimous—since the magical situation is a consensual phenomenon'—that is, magic only exists by agreement. Whether such consensual beliefs about magic, or the parental state of Manchester United supporters, are sustained depends upon the level of social development of the group deriving the belief and the personal development of individuals within that group. In the stage of Piagetian egocentrism through which we all pass (or to some extent remain) we are unable to conceive of a situation from a point of view other than our own either in terms of moral or cognitive development, and actions may follow from infantile projections foisted on to the outgroup. 'We got the boot in first!' The ingredients for change in reducing prejudicial responses induced in these ways are through personal growth, social development, and knowledge. Knowledgeable botanists will feast on the chanterelles that others scorn.

Turning to the specific case of epilepsy, consider first the curious nature of its stigma. Suddenly and without warning the individual suffers an astonishing loss of control and of developmental skills. The epileptic attack is the quintessence of the paroxysmal behaviours.[11] How might this propensity to sudden loss of status be negotiated? Perhaps in a way akin to premonitory grieving, by making declarations in word and deed between the attacks which, though of themselves stigmatising, do prepare those concerned against the catastrophe. Perhaps this might be achieved by social deference or perhaps by aggressive assertiveness There is no doubt that the import of the epileptic attack is through its occasional association with madness, deterioration, and death. Such associations need only intermittent reinforcement. Chance and Russell regarded such 'protean displays' as epileptic seizures as a form of allaesthetic behaviour, a behaviour that produces behavioural effects on other animals.[12] It is difficult to imagine what biological advantage derived from the terrifying display of tonic-clonic epilepsy, but the residue is that at least half the mothers who witness a febrile convulsion fear momentarily that their child is dying. Doctors should respond to the needs that seizures create.

In many social surveys in the West over the years since the second world war there is evidence of changes, at least of what it is regarded as permissible to say about people with epilepsy, which might become the basis of real changes of attitude and behaviour. But prejudicial responses will only diminish with real education and with social development. We have to persuade ourselves, as an effort of will, that our old, deep, prejudice needs to be controlled. Doctors spend their whole training learning to take decisions on the basis of incomplete evidence, which is in itself a prejudiced response! They also have to learn, though it is less systematically taught, to tolerate uncertainty.

"Judge not according to appearance but judge righteous judgment." John vii, 24.

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Correspondence

High plasma urea concentrations in collodion babies

Sir,

We were interested to read the paper from Drs Beverley and Wheeler [1] The authors rightly emphasise the likelihood of systemic absorption of pharmacologically active agents used topically to treat dermatoses in the neonate and report the cases of two infants born with collodion membranes who were treated with a cream containing both lactic acid and urea We were concerned to learn that such treatment had been used in neonates at all, especially in neonates with a universal erythematous dermatosis that clearly enhances percutaneous absorption. Furthermore, one of the two infants was premature, another factor known to be associated with increased skin permeability

No one involved in the medical care of infants can have any excuse for being ignorant of this problem, and we would urge the greatest circumspection when prescribing topicals for neonates In our view, the topical application of systemically active agents, such as salicylic acid, lactic acid, boric acid (used as a preservative in many topical preparations), benzene hexachloride, benzyl benzoate, corticosteroids, and certain antimicrobials, such as hexachlorophane, should be avoided in neonates Indeed, it is very rare for topical applications other than the blandest emollients to be indicated at any time during neonatal life Sadly, we still see babies in whom this precaution is ignored.

Reference

[1] Beverley DW, Wheeler D High plasma urea concentrations in collodion babies *Arch Dis Child* 1986,**61**:696–8

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Sir,

We read with interest the report of Beverley and Wheeler on the increase in plasma urea concentration during treatment of ichthyosis with a topical urea containing agent [1] We recently had a similar case on our department.

She was the first child of related (first cousin) Turkish parents, born at a gestational age of 36 weeks weighing 1960 g. She had an ichthyosiform dermatosis, which was apparent immediately after birth, but there was no collodion membrane

At first she was treated with emollient creams and during that time she had fairly constant plasma concentrations of urea, creatinine, sodium, and potassium. At the age of 46 days treatment was begun thrice daily with a cream containing 10% urea. After beginning this treatment the plasma urea concentration rose from 1·7 mmol/l to 8·4 mmol/l. There were no clinical signs of dehydration and urine production remained normal The plasma creatinine concentration remained stable and the plasma sodium concentration decreased (Figure)

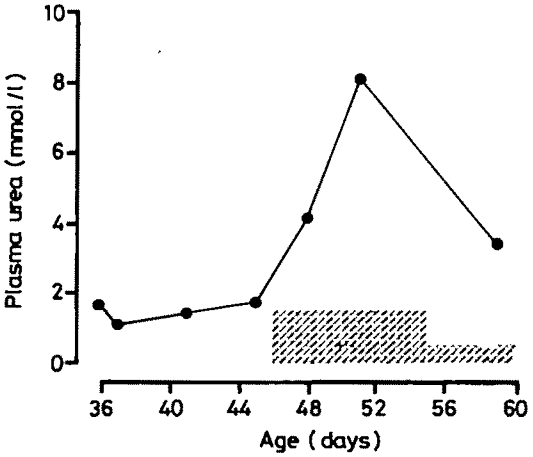

Figure *Plasma urea concentrations before and during treatment (represented by hatched area) with a topical agent containing 10% urea.*

In view of the report of Beverley and Wheeler[1] we attempted to evaluate the effect of the topical urea application on the plasma urea concentration. The use of the 10% urea cream was reduced from thrice to once daily and a concomitant drop in the plasma urea concentration from 8·4 mmol/l to 3·4 mmol/l was seen Unfortunately, the clinical condition of the baby deteriorated at this time due to septicaemia and she died soon afterwards so that we were unable to study the progress of the plasma urea concentration after total stoppage of the treatment or after possible reintroduction.

We agree with Beverley and Wheeler[1] that the effects of not only parenterally and orally administered drugs must be fully evaluated but also the effects of topically applied preparations, particularly in those patients with a defective skin barrier.

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Treatment with iron increases weight gain and psychomotor development

Sir,

Aukett *et al* have shown that Asian toddlers with iron deficiency anaemia had an increased rate of weight gain and more of them achieved the expected rate of development when treated with oral iron.[1] Although they considered the causality at some length and mention in passing that severe malnutrition is a well recognised cause of developmental delay, they do not discuss the possibility that developmental progress was secondary to improved weight rather than improved iron state. A partial correlation of developmental score on haemoglobin increase controlling for nutritional state could clarify this further. A significant correlation not explained by nutritional state would imply an independent effect of treatment with iron and would perhaps come nearer to answering their question whether 'iron deficiency anaemia may adversely effect cognitive development and behaviour' If the factors interact and there is no definite independent effect then perhaps they should state this more clearly. No one doubts that iron deficiency anaemia is worth treating. There are grey areas, however, where a small child with borderline development may have a low/normal haemoglobin It may be that energy supplements would be more suitable than iron to increase growth and development Until a trial comparing these two alternatives is performed the question will remain open

Reference

[1] Aukett MA, Parks YA, Scott PH, Wharton BA Treatment with iron increases weight gain and psychomotor development *Arch Dis Child* 1986,**61** 849–56

JOANNA POULTON
John Radcliffe Hospital,
Headington,
Oxford OX3 9DU

Drs Aukett, Parks, Scott, and Wharton comment.

We thank Dr Poulton for her interest

In previous studies we have found that extra analyses of our data suggested or performed by others have enhanced our own interpretation [1] [2] We shall see whether her suggestions can be accommodated by further analysis. We are not convinced by her subsequent arguments, however, and feel she may have failed to grasp the concept of 'pragmatic trials'.[3] Whatever the exact physiological pathway from iron supplementation to psychomotor development, the trial showed that more supplemented children achieved at least six extra skills Perhaps, as she suggests, this was because iron improved their protein energy nutrition (by an increased appetite?) and thence psychomotor achievement, although if this were so we might have expected iron deficient children in the community studied to have evidence of protein energy undernutrition as well. This was not so; indeed, the iron deficient children had some evidence of better protein energy nutrition [4]

References

[1] Viegas OAC, Scott PH, Cole TJ, Eaton P, Needham PG, Wharton BA 'Dietary protein energy supplementation of pregnant Asian mothers at Sorrento, Birmingham II Selective during third trimester only *Br Med J* 1982,**285**:592–5.

[2] Campbell-Brown M, Rossiter CE Dietary protein energy supplementation of pregnant Asian mothers at Sorrento, Birmingham *Br Med J* 1982,**285**:1579

[3] Gore S Assessing clinical trials—trial discipline *Br Med J* 1981,**283**:211–3

[4] Grindulis H, Scott PH, Belton NR, Wharton BA. Combined deficiency of iron and vitamin D in Asian toddlers. *Arch Dis Child* 1986,**61**:843–8

Inhaled beclomethasone and oral candidiasis

Sir,

I was interested to see the paper by Shaw and Edwards on 'Inhaled beclomethasone and oral candidiasis'.[1]

In that paper they stated that the incidence of candidiasis seemed to be the same whether a rotohaler or a standard aerosol inhaler was used. In my experience the standard type of inhaler is likely to deposit steroids at the back of the throat, especially when used by children

Two patients of mine regularly contract symptomatic oral candidiasis when they go on holiday and do not take with them the rather bulky Nebuhaler

I would suggest that all children having problems with candidiasis initially try some form of variation of the standard inhaler such as the Nebuhaler

Reference

[1] Shaw NJ, Edmunds AT Inhaled beclomethasone and oral candidiasis *Arch Dis Child* 1986,**61**:788–90

S E BARNES
Odstock Hospital,
Salisbury SP2 8BJ

Dr Edmunds comments·

Thank you for giving me the opportunity to see the letter written by Dr Barnes in response to our recent paper 'Inhaled beclomethasone and oral candidiasis' I was interested to learn of his experience It is important to distinguish between colonisation with candida detected by culture of pharyngeal swabs and clinically apparent oropharyngeal candidiasis Only one child among all 229 who were swabbed in our survey had clinically evident candida infection.

Our data showed that method of inhalation of beclomethasone did not influence the frequency of colonisation with candida. As clinical infection occurred only once we are not in a position to say whether or not method of inhalation influences its incidence

Serum albumin concentrations and oedema in the newborn

Sir,

Cartlidge and Rutter have provided useful data relating serum albumin concentration to gestation and discuss its poor correlation with clinical oedema [1] Their view, however, that 'hypoalbuminaemia of prematurity' is a 'normal not a pathological finding' is debatable A biochemical or clinical finding that is consistently associated with prematurity is not necessarily 'normal' and may indeed be undesirable. In this study the authors have examined only one clinical aspect of hypoalbuminaemia, oedema; yet low serum albumin concentration may have diverse effects—for instance, on drug and bilirubin binding and toxicity

Currently, we are analysing the relation between clinical outcome and plasma albumin concentration measured in over 4000 samples during a longitudinal study of 932 infants Preliminary multiple regression analysis has reaffirmed the strong association between hypoalbuminaemia and respiratory disease, even after adjustment for gestation Low plasma albumin concentration in this circumstance cannot be regarded as 'normal' and probably reflects excessive losses—for example, into alveoli—and the adverse effect of severe disease or suboptimal nutrition on protein synthesis by an immature liver Yet sick infants must have comprised an appreciable proportion of the low gestation sample investigated by Cartlidge and Rutter.

These workers contend 'that measurement of serum albumin concentrations in preterm infants, either routinely or in the presence of oedema, is of little use in their management' This conclusion might be misinterpreted A low plasma albumin concentration may be used as a marker for the high risk neonate, may influence the interpretation of other biochemical findings, and may warrant intervention in its own right Albumin estimation is cheap and, I believe, should not be abandoned as a routine investigation in very low birthweight infants in the neonatal period

Reference

[1] Cartlidge P, Rutter N Serum albumin concentrations and oedema in the newborn *Arch Dis Child* 1986,**61**:661–5

A Lucas
*University of Cambridge
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Cambridge CB4 1XJ*

Drs Rutter and Cartlidge comment

We agree with Dr Lucas that a finding consistently associated with prematurity is not necessarily normal We found though that serum albumin was a poor marker of illness in low gestation infants: concentrations were low in both sick and well infants. His unpublished study clearly contains many more infants and we look forward to seeing it We still contend that routine measurement of serum albumin is of little use in the management of the preterm infant. Certainly, bilirubin and drug binding are affected by low serum albumin concentrations, but routine measurements are not carried out with this in mind. Perhaps a case can be made for routinely measuring albumin whenever serum calcium concentrations are measured in the preterm infant. Hypocalcaemia is commonly diagnosed and treated on the basis of low uncorrected calcium concentrations, but it is largely an artefact caused by a low serum albumin concentration.

Minimal change nephrotic syndrome and cyclophosphamide

Sir,

The interesting annotation by Trompeter about minimal change nephrotic syndrome and cyclophosphamide rightly indicates that the use of alkylating agents is controversial in a 'non-malignant condition with an excellent long term prognosis' [1]

The point is well made that an increased risk of malignant disease after immunosuppressive drugs has been observed in both adults and children, but this is perhaps too broad a generalisation. It is possible to go further. Cyclophosphamide, chlorambucil, and nitrogen mustard all undoubtedly cause secondary leukaemias,[2 3] Other immunosuppressive agents, such as methotrexate or azathioprine, apparently do not In other words not all cytostatic immunosuppressants carry the same risk of inducing neoplasia. While I appreciate that they may not have an equivalent therapeutic effect either, nevertheless it is an important point that should be borne in mind by clinicians who may be tempted to prescribe one for any benign disorder

J S Lilleyman
*The Children's Hospital
Sheffield*

References

[1] Trompeter RS Minimal change nephrotic syndrome and cyclophosphamide *Arch Dis Child* 1986,**61**:727–9
[2] International Agency for Research on Cancer *Monographs on the carcinogenic risk of chemicals to humans* Suppl 4 Lyon IARC, 1982.
[3] Rosner F, Grunwald H Cytotoxic drugs and leukaemogenesis *Clin Haematol* 1980,**9**:663–81

High dose intravenous methylprednisolone in treatment of recessive osteopetrosis

Sir,

The paper of Dorantes *et al*[1] gives me an opportunity to report my results in treating recessive osteopetrosis with high dose intravenous methylprednisolone, which partially support their results

Three infants, a 4 month old girl, a 5 month old boy, and, more recently, a 14 month old girl, with typical recessive osteopetrosis were treated with intravenous methylprednisolone in doses of 30 mg/kg/day for three days, 20 mg/kg/day for four days, and subsequently 10, 5, and 2 mg/kg/day for one week each, respectively, followed by 1 mg/kg/day until their haemoglobin concentration reached 11 g/dl, as described previously in the treatment of childhood acquired aplastic anaemia[2] Haemoglobin reached this concentration in 34, 62, and 194 days, respectively

Liver and spleen became normal in size, with rises in leucocyte and platelet counts and haemoglobin concentrations to normal, a decrease in reticulocyte count, and disappearance of normoblastaemia in the first two cases and improvement in the third child The patients' plasma haemoglobin concentration and alkaline phosphatase activity decreased to normal, with normalisation of haptoglobin concentrations Their bone marrow became normocellular as studied by needle aspiration, but their bones have not been influenced by treatment yet according to findings on *x* ray film.

Although currently one child could only detect light and still had mild exophthalmus and all had macrocrania, their growth and development were appropriate for their ages The two younger cases still required 2·5 mg prednisone daily and the third was currently on intravenous treatment. With the exception of Cushingoid appearance during high dose administration, they did not have any side effects of treatment with corticosteroid, such as hypertension, hyperglycaemia, or growth retardation.

I would also like to question the laboratory findings of the authors' second case, who had a normal (or raised) haptoglobin concentration (5 mg/dl), despite pronounced plasma free haemoglobin (125 mg/dl), which does not agree my findings or expectations

References

[1] Dorantes LM, Mejia AM, Dorantes S Juvenile osteopetrosis effects on blood and bone of prednisone and a low calcium, high phosphate diet *Arch Dis Child* 1986,61:666–70.

[2] Ozsoylu §, Coşkun T, Minassazi § High dose intravenous glucocorticoid in the treatment of childhood acquired aplastic anemia *Scand J Haematol* 1984;33.309–16

§ OZSOYLU
Institute of Child Health,
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Diamond Jubilee issue

Sir,

The Diamond Jubilee issue of the *Archives* provided fascinating accounts of those who over the years have guided it to its present state of eminence as a paediatric journal. Three citations were omitted—namely, those of the present editors Roy Meadow and Bernard Valman and the associate editor Malcolm Chiswick. While we recognise and respect their modesty, we should not let the occasion pass without acknowledging the very important part which they have played in maintaining and enhancing the position of the *Archives* To Roy Meadow, who will shortly be giving up the senior editorship, we owe a particular debt of gratitude.

JOHN FORFAR
British Paediatric Association,
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Working party on cystic fibrosis

Sir,

In Dr Jackson's synopsis of the recent report of the British Paediatric Association working party on cystic fibrosis mention is made of the proposal 'that there should be one centre with from 50 to 100 patients in most regions'.[1] In some National Health Service regions it is clear that more than one cystic fibrosis centre will be needed so perhaps the proposal should be amended to 'at least one centre with from 50 to 100 patients in most regions' The staffing levels suggested for a clinic with 50 patients should, of course, be increased pro rata for larger clinics.

Reference

[1] Jackson ADM Working party on cystic fibrosis *Arch Dis Child* 1986,61:724.

JOHN A DODGE
Chairman,
BPA Working Party on Cystic Fibrosis

Archives of Disease in Childhood, 1987, 62, 216

Book reviews

Epilepsy in Children. (International Review of Child Neurology Series). By J Aicardi. Pp 413 $74·50 hardback Raven Press, 1986

It is a privilege to review this single author masterpiece on childhood epilepsy

The volume is divided into four parts. It begins with a common sense discussion of the meaning of epilepsy, a definition of terms, the effect of age, and classification of epileptic seizures and epilepsies.

The second part deals individually and critically with the best established epilepsies and epileptic syndromes, emphasising the clinical seizure descriptions and electroencephalographic features necessary for giving treatment and prognosis, infantile spasms and such like, Lennox-Gastaut syndrome and early myoclonic epilepsies, later childhood myoclonic epilepsies, progressive myoclonic epilepsies, epilepsies with typical absences, epilepsies with generalised tonic-clonic seizures, epilepsies with simple partial seizures (including the benign epilepsies), epilepsies with partial complex and affective seizures, and the syndrome of 'acquired aphasia' (too often diagnosed as elective mutism!)

In the third section the perspective is altered to consider epileptic manifestations in relation to age, duration, 'cause', and precipitation, with chapters on neonatal seizures, epilepsy in infants (still a goldmine for future research), febrile convulsions, other occasional convulsions, status epilepticus, stimulus sensitive epilepsies, post-traumatic epilepsy, and epilepsies as the presenting manifestation of brain tumours.

The fourth part deals with selected aspects of diagnosis and differential diagnosis (including a critical analysis of anoxic seizures) and general aspects of prognosis and treatment that have not been covered already when discussing specific epilepsies or clinical situations

Sixty pages of the book are devoted to the bibliography, which is serially numbered in alphabetical order Dr Aicardi states that he has attempted whenever possible to limit the review of the publications to books or articles of general interest that can serve as an introduction to further reading Since one of the justifications of the book is the pooling together of information often available only in esoteric books, journals, or conference proceedings, however, it is no surprise that the references total around 1600 References up to 1986 are included, and some are 'in press'

My only serious criticism is of the index, which was not compiled by the author himself It is by no means brief, having 880 entries, but even so several items either are missing from the index or irritatingly require looking up under several headings to find an entry This problem derives from the immense wealth of material in the book and could be corrected in a future edition Meanwhile, readers should not be put off if they wish to find the answer to an unindexed question—if necessary, read the book from cover to cover (again).

Doctors who treat children with convulsions or epilepsy should have this book both on their own shelves and in their departmental libraries

J B P STEPHENSON

Nutrition and Growth in Infancy and Early Childhood. By N E Hitchcock, M Gracey, A I Gilmour, and E N Owles Monographs in Paediatrics No 19. Pp 92: £31.00/SFr 79·00/DM 95·00/US $44 00 hardback. Karger, 1986.

This well presented though rather brief monograph summarises the results of a five year prospective longitudinal study, known as the Perth growth study, which followed growth and development in a homogeneous sample of 205 full term infants selected from a well nourished community. The book describes feeding practices, energy and nutrient intakes, growth centiles, development, dentition, and morbidity from birth to 5 years of age

The sample contained a larger proportion of families from high social ranks compared with the Western Australian population, but the authors defend their selection criteria on the grounds that their objective was to study infants living in an environment conducive to good health. While most infants were breast fed, unfortunately breast milk volumes were not measured so that nutrient intake calculations, which were restricted to foods that did not contain breast milk, sadly do not provide a complete picture Duration of breast feeding had no significant protective effect against minor infection (documented by the mothers), probably because few children in the study lived in disadvantaged circumstances

Numerous publications have already emerged from the Perth growth study, though this volume does represent a convenient summary of findings over the whole five years Nevertheless, 92 pages is a small output from such a major endeavour. Detailed statistical analyses are not presented While each chapter includes discussion of results, there is only brief mention of other, similar, longitudinal studies conducted in various parts of the world over past decades, and this does limit the educational value of the book.

This monograph has a high price for its size, but it is required reading for anyone entering the debate on the effects of early diet and growth. The Perth children will provide a valuable yardstick against which future generations can be assessed.

ALISON PAUL

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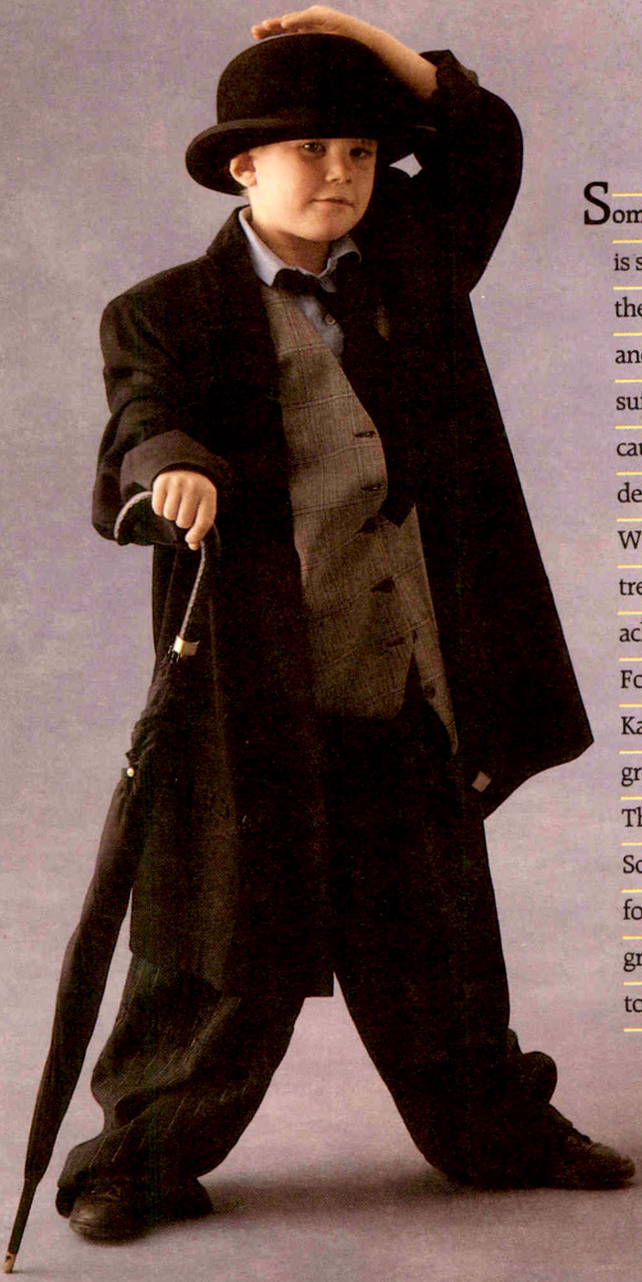

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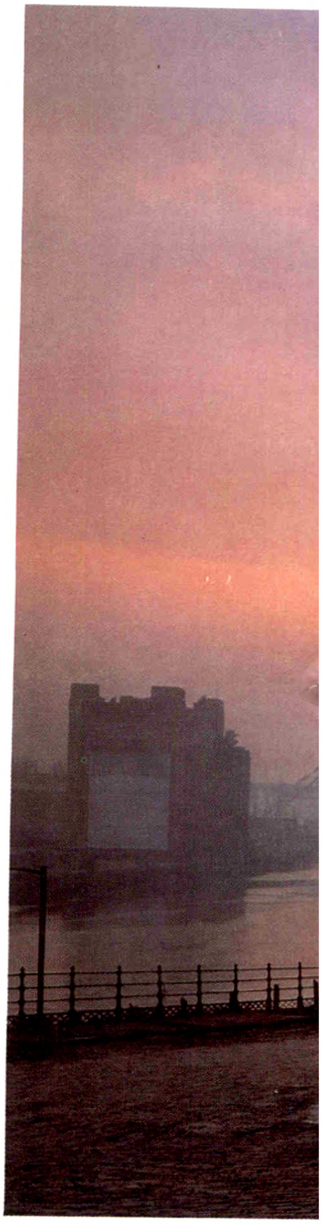

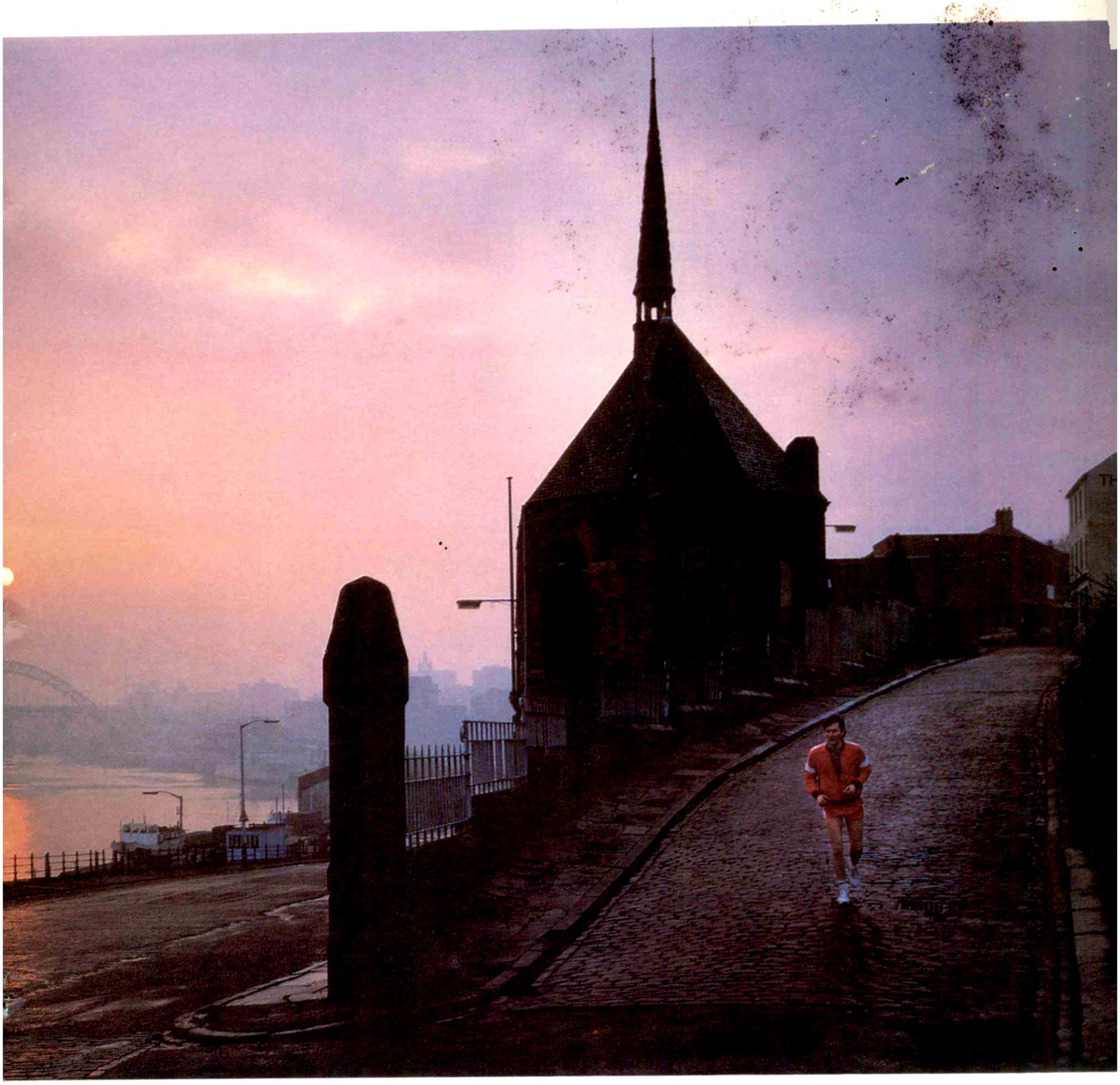

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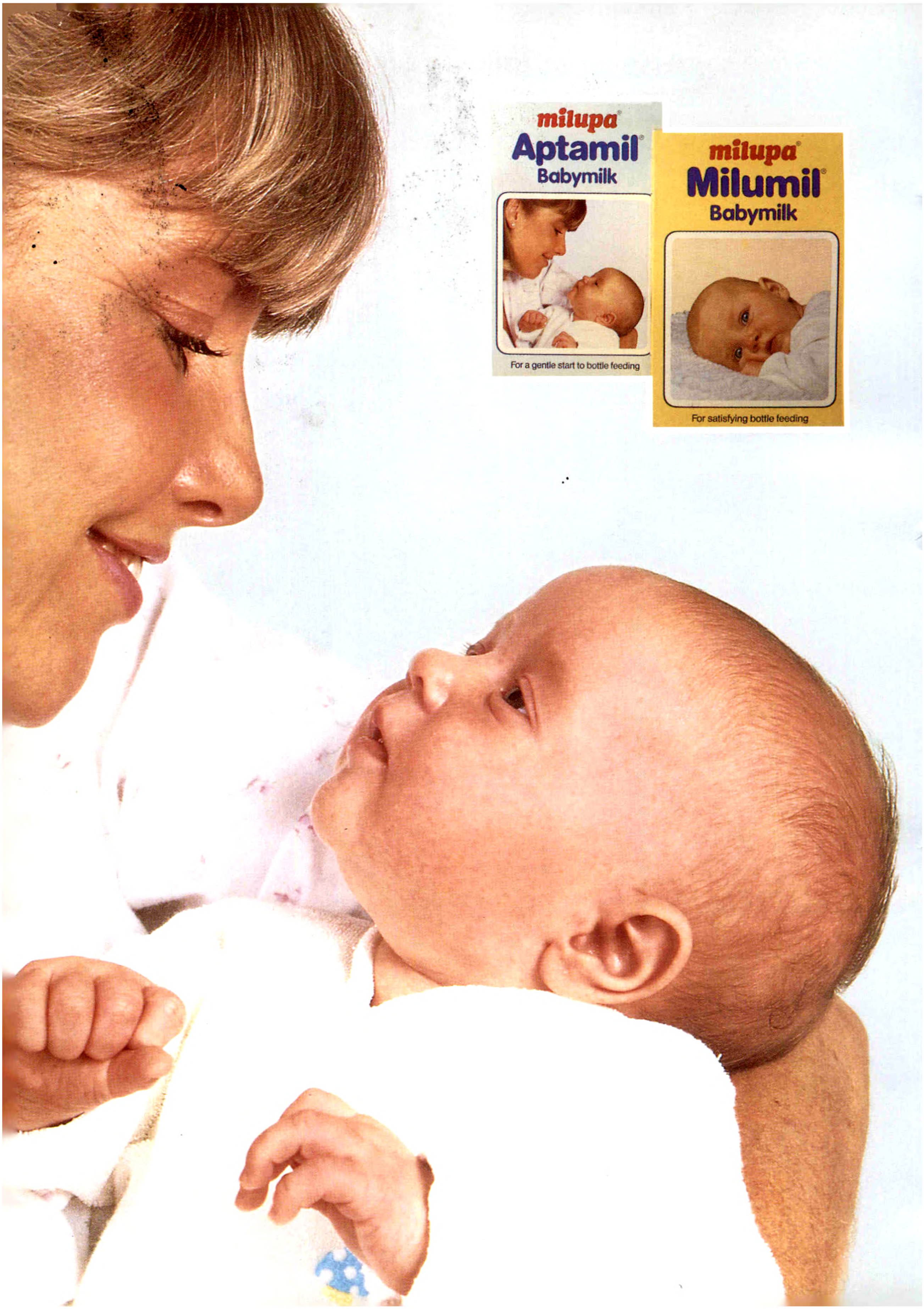
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Archives of Disease in Childhood, 1987, **62,** 217–219

Annotations

Who needs the clinical geneticist?

General paediatricians face the increasing constraints of specialisation on their practice. Now next in line comes the clinical geneticist. Is he to be accepted as an ally and trusted colleague? Does his position, now firmly established on the medical scene, imply that only he is qualified to talk about the genetics of disease and counsel parents about the future? If he really believes that, what exactly is it that he can offer that is not easily found in the books of Harper,[1] Emery and Rimoin,[2] and McKusick?[3]

Fortunately, the calculation of recurrence risks is not the sole prerogative of the clinical geneticist, nor is it his only function. In practice, the clinical geneticist, like any other consulting colleague, will answer questions on the telephone, see children when asked, and talk to and give advice to parents on request. In some genetic clinics the geneticist sees children and parents alone, in others jointly with the paediatrician When that happens the paediatrician remains in control and, having been witness to what has been said, is later in a better position to go over the ground, correcting misunderstandings and helping parents to reach decisions In certain situations—to be made clear—the geneticist is likely to retain a distinct advantage over other clinicians, but the nature of that superiority will change as probabilities become fact and new techniques revolutionise our understanding of malformation and genetic disease

The advantages that the geneticist has over the paediatrician are there to be exploited. The list includes a knowledge of genetic disease and its behaviour within families; a preparedness to examine such families as well as individuals; an understanding of biochemical and chromosomal genetics; a trained approach to the evaluation of malformation and dysmorphic signs; and a direct involvement with new laboratory techniques that will identify genetic disease. His position is central between the general practitioner, paediatrician, obstetrician, and other clinicians and investigators. He is supported by trained nursing staff who organise and attend clinics, maintain registers, visit, advise, and follow up families, and ensure that complex information discussed in clinics is understood. But with which families, and when, should he become involved? The answer depends on three factors. the needs of the parents, the nature of the disease, and the ability of the paediatrician to provide the answers.

Malformation

As isolated malformations are rarely the end result of a single mutant gene the risk of recurrence should always be low: it is, nevertheless, in most cases increased both for sibs and children. The most likely explanation is that polygenic or multifactorial influences are playing a part. For such isolated cases without obvious cause, the paediatrician will find that Harper's 'Practical genetic counselling'[1] provides all the information he needs about recurrence risk once he has satisfied himself that there are no suspicious trends in the family The risks are generally small and, if given early, are reassuring to parents, who are bound to be exposed to misleading, inaccurate, and unsolicited information in due course. Later on, parents may ask about prevention, as for neural tube defect, and the value, nature, and accuracy (as well as the risks) of tests that may be available in pregnancy. Oral or written advice from the geneticist should be sought at this stage.

When there is clustering of similar malformations in the family or sibship the risk of recurrence is higher Sometimes this is because single mutant genes are operating as in Van der Woude's syndrome (cleft lip or palate with mucous cysts of lower lip, or both) or in the inherited form of encephalocoele (Meckel-Gruber syndrome), but there are less well defined situations for which risk figures are rarely available. Such families are better referred

Multiple malformations and the dysmorphic syndromes

The geneticist also comes into his own when he is asked to define the future for the child with multiple malformations and determine whether the combination is fortuitous, familial, or the result of association (such as vertebral defects, imperforate anus, tracheo-oesophageal fistula, and radial and renal dysplasia) or sequence (as in Robin's syndrome) and so determine the chance of recurrence Geneticists should be invited to see abnormal children in the newborn period as a matter of course if the diagnosis cannot be established immediately Early answers can avoid the need for expensive investigations, but, even when a solution is not readily obtained, the sequence of these investigations can be logically determined. The geneticist's opinion is also of value to neonatal surgeons and cardiologists, who will want to know what the eventual outcome may be when advising parents and planning costly life saving and time consuming surgery.

In the last few years the delineation of rare malformation syndromes has achieved stupendous growth. Each new consultant clinical geneticist is now expected to have completed a formal training in the technique of visual dissection of these conditions, which is essential to achieve diagnosis. The interest is not effete for important questions about prognosis, and recurrence risks need to be answered and, in addition, firm labels, once applied, may help to lighten the burden of guilt that parents carry.

No one pretends that the diagnosis of the dysmorphic child is an easy challenge. When Smith[4] has been perused and a chromosomal cause excluded one approach is to interrogate the computerised data base for the diagnosis of rare dysmorphic syndromes.[5] In 1984 this contained information on about 700 syndromes accompanied by 1500 references gleaned from works published in the previous 15 years. By 1986 Baraitser and Winter had enlarged the 'London dysmorphology base' to include 1400 syndromes and 4500 references. (Baraitser M, Winter RM. Personal communication.) The authors have now added a facility that will allow new clearly defined 'unknowns', which have foiled panels of experts, to be included and later matched with others. Many genetic units already have copies of the dysmorphology base and have learned the tricks of interrogation. Nevertheless, even with this advance, a diagnosis may not be reached. This is particularly so when the child, retarded and with unusual facies, has no 'hard' signs, such as cleft palate or congenital heart disease, as signposts for the computer search. Frustrating as it still is, a careful assessment by the clinical geneticist remains the best approach to these problems.

Single gene defects

Paediatricians have always undertaken the responsibility of telling parents when their child's illness was the result of autosomal recessive inheritance, explaining the risks of recurrence and the consequence of the illness. Are they still competent to do this? In most cases the answer is 'yes', though in some cases they will ask either a colleague with special knowledge and experience of that disease to see the parents.

The immediate question for general paediatricians is whether organ or disease specialists, rather than geneticists, should be responsible for counselling many families with single gene disorders, especially those dealing with kidney, blood, and inborn errors of metabolism. In most instances the former will know more about the natural history of the disease and its behaviour within families than the geneticist, but he should be called in to advise on antenatal diagnosis and its coordination or to talk about the more difficult options, such as artificial insemination by donor. The same argument can be extended to include the nervous system, the ear, and the eye, but, in practice, counselling families with diseases that affect these systems is best provided by specialist and geneticist working together in the same clinic.

Whereas most doctors can explain the nature of the recurrence risks to parents of children with cystic fibrosis, calculations for risks further out in the family should be given with caution and preferably after checking the calculations with the geneticist. How many can calculate the risk of cystic fibrosis to the first cousin of an affected child (incidence of carriers in the population 1/20)? On a local course only six of 100 selected candidates for the part 1 MRCP examination obtained the correct answer of 1/160.

When the child's illness is a serious one the paediatrician does not hesitate to introduce information about its genetic basis and risks of recurrence. Explanations at this stage have to be presented clearly and simply but in such a way that parents will ask for more details later on. This is particularly important if a deleterious autosomal dominant or X linked recessive gene is responsible. The question then is whether the mutant gene lies hidden in the parent. When there is doubt the geneticist will examine or investigate the parents appropriately and, if necessary, look further into the family background. But what should the paediatrician do when he recognises an important disorder that is inherited as an autosomal dominant as part of a routine examination for some unrelated complaint, and where does the geneticist fit in there? Neurofibromatosis is a good example. In a proportion of children this is responsible for serious problems early in life, but most affected children are asymptomatic. The paediatrician remains the best judge of what should be said at the time, but should not the clinical geneticist be asked to talk about the disease, examine the parents, and describe how it may affect other members of the family differently at some later stage? The conundrum is how to balance the giving of unsolicited information without producing anxiety that then cannot be allayed. This difficulty is one that is ever present and to which the geneticist is more than sensitive.

Investigation of families

The difference between paediatricians and geneticists is that the former pride themselves with working with the family, the latter in investigating families. How many paediatricians are prepared to carry out the detailed examination of parents or have the facilities or time in their clinics to do so? There may be exceptions, such as in tuberous sclerosis or the examination of the urine in family members where Alport's syndrome is suspected. But who wants to arrange for the systematic collection of family bloods for chromosomal analysis and is then prepared to counsel the carriers, and how many know what subtle signs to seek in the rarer dominantly and X linked inherited disorders?

Carrier detection

Is the paediatrician competent to determine who is a carrier for a genetic disease? For diseases such as the haemoglobinopathies, where the investigation gives precise definition, there is no difficulty, but, when the interpretation of investigation is less exact and where pedigree analysis plays a part, as for linked disease, the problem must be referred. Bundey showed in 1978 how badly geneticists in the United Kingdom fared when asked to calculate the risks of families with Duchenne muscular dystrophy.[6] They, at least, have now learned their lessons. DNA studies do now play a part in determining carrier state, but they are only of value to a small number of families. For the present, therefore, the calculation of odds remains a most useful method.

Registers

Should registers, dear to the heart of so many geneticists, be feared by paediatricians? Should their patients be included and, if so, for what benefit and at what cost? At present, registers of families with Duchenne muscular dystrophy are commonplace: they also exist for families with balanced chromosomal translocations and, lesser sophistication, for Huntington's chorea, polyposis coli, and familial polycystic kidney. The register is controlled by the geneticist and operated by nurse fieldworkers, whose job is to keep in touch with families, offer carrier detection tests, and, when appropriate, genetic counselling. Confidential records, whether on file or on disk, are kept under lock and key and only reached through the clinical geneticist. The keeping of such registers and the counselling of more distant family members are not part of the paediatrician's remit nor should he seek it unless he wishes to be the 'key person', when the genetic emergency—pregnancy—presents.

DNA

β Thalassaemia, Duchenne muscular dystrophy, haemophilia A, and cystic fibrosis are the main childhood diseases where DNA studies can provide a way of deciding accurately whether a fetus is affected. The current position with Duchenne muscular dystrophy, while regional laboratories are set up and funded, is that bloods from children and their parents should be channelled through the geneticist, who will arrange for storage, analysis, reports, and maintain a central DNA record. The last is essential for rapid recall at time of pregnancy, especially if chorion villus sampling examination is envisaged. In the cases of cystic fibrosis and β thalassaemia the time will soon arrive when the records, interpretation, and advice will be best dealt with by the special clinic dealing with that particular disease, but X linked disease may well remain the exception because of the continued participation, testing, and counselling of female members of extended families through the register and the genetic fieldworkers.

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Archives of Disease in Childhood, 1987, **62**, 220–221

Drug absorption through the skin: a mixed blessi

Skin is a barrier that keeps body water in and microorganisms and noxious chemicals out. Topical drugs, the mainstay of treatment in dermatology, are applied in the hope and expectation that any percutaneous absorption will be minimal and that systemic side effects will not occur It is becoming apparent though that skin is not quite as impermeable as often believed. Undoubtedly, drugs can be absorbed through the skin and produce either unwanted or intended systemic effects

Mechanism of percutaneous absorption[1]

The superficial layers of the epidermis, the stratum corneum, provide almost all the skin's barrier properties. (The basal epidermal layers and the underlying dermis are readily permeable—the often used term 'transdermal absorption' is inaccurate) The stratum corneum is made up of layers of overlapping cell plates containing the fibrous protein keratin. Most drug absorption is transcellular. it is unlikely that noticeable absorption occurs between cells or through sweat pores and hair follicles. It is a passive diffusion process, the magnitude of which will depend on the integrity and efficacy of the epidermal barrier but which will be influenced by the drug itself Drugs with low molecular weight (below 800 daltons) with a high water and lipid solubility show the greatest penetration. The vehicle that contains the applied drug is important So too is the degree of hydration of the stratum corneum: occluding the epidermis increases its water content, enhancing drug absorption.

Paediatric considerations

Size. The smaller the child the larger the surface area relative to body weight. Absorption of drugs depends on the surface area exposed, whereas distribution, metabolism, and excretion relate more to weight. Percutaneous drug absorption is therefore more important in a very low birthweight infant than in an older child.

Integrity of the epidermis. Percutaneous absorption is greatly increased if the epidermal barrier is damaged or diseased. Young children with burns and infants with extensive skin disease (particularly eczema) are therefore at risk.

Maturity of the epidermis. The stratum corneum is well developed in the term infant and has similar barrier properties to those of a child or adul poorly developed in preterm infants, partic those with gestation less than 28 weeks.[2] infants have a very high transepidermal wat and readily absorb topically applied agents, times with disastrous consequences. Immatu the stratum corneum is only temporary. T trauterine environment triggers rapid matur so that by 2 or 3 weeks of age the skin has s barrier properties to that of a term infant.

Hazards of percutaneous absorption

In 1886 Dr W Rayner, visiting medical officer Marylebone Workhouse, London, reported a break of cyanosis in newborn infants.[3] He fo image of the workhouse stamp used for mark nappies imprinted on the buttocks and vulva of the infants and correctly deduced that som in the ink (an aniline dye) was being absor cause cyanosis (methaemoglobinaemia). His sage went unheeded and at least nine f outbreaks of methaemoglobinaemia cause absorption of aniline dyes have been reporte considerable mortality.

Reports of other drugs and chemicals absorbed through the skin and causing toxic are numerous. Most involve dermatological arations and topical antiseptics, not surprisi such agents are often liberally applied to larg of the skin of infants.

Dermatological preparations. Systemic effect the absorption of topical steroids have ofte reported. Most affected are young infant extensive eczema treated with powerful fluo steroids. Effects range from adrenal suppres reduced growth and frank Cushingoid featu solution of 1% hydrocortisone does not se produce these effects and is therefore safer treatment of eczema in infants. Many other agents have been reported to be absorbed t the skin, causing toxic systemic effects. Perh most notable is the aminoglycoside neomycin, is never used systemically because of ototoxi is often used in the form of a triple antibiotic spray (with polymixin and bacitracin), which liberally on damaged skin can be absorbed

Topical antiseptics. Hexachlorophene was used as a topical antiseptic for the preven staphylococcal infection in the newborn. years it was common practice for infants bathed in it. Animal toxicology studies showed that central nervous system damage occurred, with a characteristic intramyelin oedema and vacuolation, but it was assumed that it was safe in the newborn infant because blood concentrations were so low. Toxicity was only reported in infants with damaged or diseased skin. When preterm infants were studied, however, it was clear that absorption was much greater, and brain lesions identical to those seen in poisoned animals were identified in 17 out of 248 infant autopsies.[4] Common features of these 17 infants were prematurity and repeated exposure to hexachlorophene. Tragic confirmation that hexachlorophene is neurotoxic after percutaneous absorption came when a French manufacturer accidently marketed a batch of baby talcum powder that contained 6·3% hexachlorophene (it should have contained none). Altogether 204 infants were poisoned, with an illness characterised by a severe ulcerating nappy rash, fever, convulsions, and coma, of whom 36 died.[5]

Iodine and alcohol cause local and systemic effects, and although chlorhexidene is thought to be safe it is certainly absorbed through the immature skin. Poisoning from topical absorption of drugs and chemicals should always be borne in mind by staff who care for infants below 28 weeks' gestation. The skin is such a poor barrier that topical application is similar to oral administration. The very immature infants are usually sick and often die; tragedies such as have happened to older infants could easily be ascribed to natural illness and pass unnoticed.

Uses of percutaneous absorption

Drugs can be topically applied for local or systemic effect.[6]

Local effect. The use of local anaesthetic cream is a welcome innovation. Usually, drugs like lignocaine are poorly absorbed and do not produce local anaesthesia. A new preparation, a eutectic mixture of 2·5% lignocaine and 2·5% prilocaine as an oil water emulsion, is absorbed appreciably when placed under an occlusive dressing. It produces very good local anaesthesia in children. The cream (EMLA cream, Astra Pharmaceuticals Ltd) is particularly useful for children who need a venepuncture. Disadvantages are that it has to be applied an hour in advance and that the cream under the occlusive dressing is rather messy and is expensive (about £1 a time), but these are outweighed by the pain children are spared. An alternative preparation suitable for the poorly developed skin of a preterm infant would be welcome in the neonatal intensive care unit.

Systemic effect. If a drug can exert its effects in minute dosage the small amount absorbed through the skin may be sufficient for systemic effect. A number of drugs can be administered to adults through the skin—namely, nitroglycerine for angina, hyoscine for travel sickness, clonidine for hypertension, and oestrogens for replacement therapy (only nitroglycerin is available in the United Kingdom). The drug delivery system is in the form of an adhesive patch, containing (from the outside to the skin surface) an occlusive backing, a reservoir of the drug, a microporous membrane, and an adhesive. The microporous membrane is less permeable to the drug than the skin and is therefore rate limiting, releasing the drug in a controlled way. Such a method of drug administration is not simply a curious gimmick. It is convenient, requiring less frequent dosage than oral administration, produces more predictable and constant blood concentrations, can be taken by vomiting patients, and can be removed at once Unfortunately, most drugs given chronically to children (anticonvulsants, antibiotics, and bronchodilators) require too high a dose to be effective through the percutaneous route.

Where percutaneous treatment with drugs may have a part to play is in the treatment of the preterm infant. Small size and immature skin mean that a drug such as theophylline, which could not be given topically to a child, is readily absorbed and reaches therapeutic blood concentrations.[7] Oral treatment with drugs in the small sick infant is unreliable and often contraindicated, while intravenous treatment requires skilled staff to establish and maintain it and is more hazardous and painful. Development of drug delivery systems that would enable preterm infants to be treated through the skin is an exciting possibility.

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Original articles

Growth hormone state after completion of treatment with growth hormone

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SUMMARY After completion of treatment with growth hormone (GH) 19 patients with isolated 'idiopathic' GH deficiency and 15 with post-irradiation GH deficiency underwent retesting of GH secretion with an insulin tolerance test or an arginine stimulation test, or both. Patients with post-irradiation GH deficiency comprised 13 patients with central nervous system tumours distant from the hypothalamo-pituitary axis and two with acute lymphoblastic leukaemia, who had received cranial or craniospinal irradiation.

All 15 patients with post-irradiation GH deficiency remained GH deficient (peak GH response <7 mU/l (n=10) and 7–15 mU/l (n=5)). Of the 19 retested patients with idiopathic GH deficiency, however, five (26%) had peak GH responses of >15 mU/l (regarded now as transient or false idiopathic GH deficiency) and were indistinguishable from the remainder (permanent or true idiopathic GH deficiency, peak GH responses <7 mU/l (n=12) and 7–15 mU/l (n=2)), by pretreatment anthropometry and post-treatment height standard deviation score, but had a lower first year height velocity (mean (SD) velocity 5·6 (0·5) cm/year for false idiopathic deficiency *v* 8·7 (1·75) cm/year for true idiopathic deficiency, p<0·01) and height increment on treatment (mean (SD) increment 2·2 (1·5) cm/year for false idiopathic deficiency *v* 5·2 (2·3) cm/year for true idiopathic deficiency, p<0·05). By current practices two patients with false idiopathic deficiency may have been distinguished by sex steroid priming.

Thus post-irradiation GH deficiency seems to be permanent, but errors in diagnosis in idiopathic GH deficiency are common.

Growth hormone (GH) was first introduced for the treatment of GH deficiency in 1958,[1] and there is no doubt of its efficacy.[2] The question of who should receive treatment with GH, however,[3–6] has been broadened, concurrent with the availability of biosynthetic GH. GH deficiency may no longer be a prerequisite for treatment, as it has been suggested that constitutionally short children[7–9] or girls with Turner's syndrome[10] may benefit from its use, though long term side effects in such groups have not yet been evaluated.[11]

As the scope for treatment with GH widens it is of interest to evaluate those criteria that are used conventionally to confirm the diagnosis of GH deficiency.[12] These criteria will not encompass those patients who produce adequate GH to pharmacological stimuli but do not exhibit normal 24 hour GH production under basal circumstances[13] nor those with a bio-inactive form of endogenous GH,[14] whose growth accelerates with exogenous GH

Errors in diagnosis have been recognised in patients with isolated 'idiopathic' GH deficiency, who may be indistinguishable auxologically and biochemically from the constitutionally short child with delayed development.[15] There has also been argument about the need for treatment with GH in children with radiation induced GH deficiency, who, it has been suggested, may pass through a transient state of GH deficiency that is insufficient to affect long term growth.[16 17] In an attempt to audit the success of current diagnostic criteria we have studied GH secretion in patients diagnosed as GH deficient initially and in whom treatment with GH has been completed.

Patients and methods

Since the inception of the north west regional growth clinic in 1972, 69 children (44 boys and 25 girls) have received and completed a course of treatment with GH. The categories of patients

Table 1 *No of cases retested in each diagnostic category of patients with growth hormone deficiency and outcome of retesting*

Diagnostic category	*No of cases*	*On retesting*		
		Diagnosis confirmed	*Diagnosis refuted*	*Not retested*
Craniopharyngioma	12	3	0	9
Other central nervous system tumours	24	15	0	9
Panhypopituitarism	5	3	0	2
Isolated growth hormone deficiency	28	14	5	9

reported and studied were craniopharyngioma (n=12), central nervous system (CNS) tumours (n=24), panhypopituitarism (n=5), where there is a deficiency of more than one anterior pituitary hormone, and isolated GH deficiency (n=28).

A full reassessment of GH secretion was performed in 40 children (26 boys and 14 girls) six months after they had completed their treatment with GH (Table 1) The group with CNS tumours consisted of 13 patients with cerebral tumours distant from the hypothalamo-pituitary axis and two cases of acute lymphoblastic leukaemia, all of whom received cranial or craniospinal irradiation as part of their treatment.

The initial biochemical confirmation of GH deficiency was based on the following provocative and physiological tests of GH secretion (placed in order of frequency of usage). insulin tolerance test, arginine, Bovril, sleep, glucagon, and clonidine stimulation. At least two tests of GH secretion were carried out on each patient, and both results had to concur to support a diagnosis. Total GH deficiency was diagnosed if the peak GH concentration was <7 mU/l, partial deficiency if the concentration was 7–15 mU/l, and normal GH secretion if the concentration was >15 mU/l. In 1981 sex steroid priming was introduced for patients whose bone ages were greater than 10 years. GH was assayed by double antibody radioimmunoassay in a single laboratory, which had participated in the United Kingdom external quality assurance scheme since 1976

Auxological criteria for a diagnosis of GH deficiency were growth velocity, measured at the growth clinic over one year, below the 25th centile, a standing height more than 2·5 standard deviations below the mean for age and sex, and satisfactory general, auxological, and endocrine evidence to exclude or define any complicating factors [12]

A diagnosis of GH deficiency was made on these grounds and the data presented to the health services human growth hormone committee, which authorised the release of pituitary extracted GH for treatment. At the end of the first year of treatment an increase of 2 cm on the pretreatment height velocity was considered an acceptable response and worthy of continuing treatment.

In most of the 40 patients in whom GH state was reassessed an insulin intolerance test or arginine test, or both, was performed. Peak GH concentrations, as defined above, were used to confirm or refute the original diagnosis.

For those patients in the group with idiopathic GH deficiency, auxological variables before, during, and after treatment were compared between those in whom the diagnosis of GH deficiency was confirmed or refuted. Statistical methods consisted of Student's t test (two tailed) for those values distributed normally and Mann-Whitney U test for those that were not. Predicted heights at the start of treatment with GH were evaluated using the formulas of Tanner and Whitehouse.[18]

Results

Tumour groups. All patients whose GH deficiency resulted from craniopharyngioma or its treatment

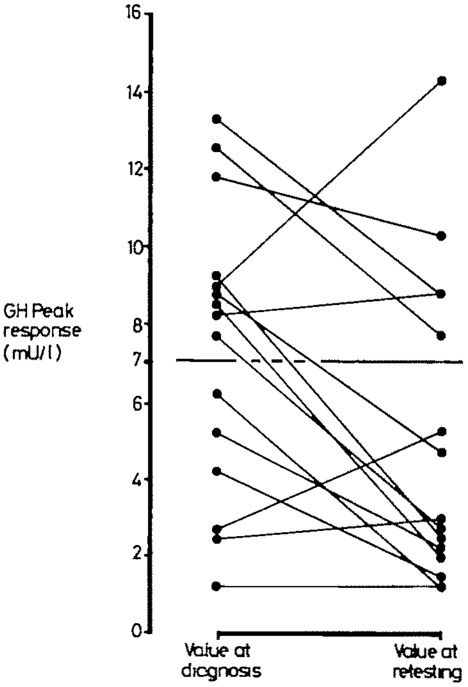

Figure *Growth hormone (GH) peaks after an insulin tolerance test or arginine provocation at initial testing and on retesting after stopping of treatment with GH in the group with post-irradiation GH deficiency Mean (SD) GH peak at diagnosis was 7·2 (3 5) mU/l and at retesting was 4·8 (4·0) mU/l* (n=3) or from radiation induced damage to the hypothalamo-pituitary axis after treatment for acute lymphoblastic leukaemia (n=2) or a cerebral tumour distant from the hypothalamo-pituitary axis (n=13) were still GH deficient on retesting. At diagnosis and on retesting the three patients with GH defiency due to craniopharyngioma had peak GH concentrations <7 mU/l. At diagnosis, six of the patients with post-irradiation GH deficiency had peak GH concentrations <7 mU/l, and nine fell in the partial range (7–15 mU/l). On retesting, however, 10 were totally and five partially GH deficient (Figure). Thus four patients initially diagnosed as partial had become totally deficient on retesting. The mean (SD) interval between diagnosis of tumour and start of treatment with GH for these patients with post-irradiation GH deficiency was 5·5 (3·2) years (range 1·3 to 10·9 years) and from diagnosis to retesting was 10·5 (3·6) years.

Panhypopituitarism. All three patients were totally GH deficient (peak <7 mU/l) both before and after treatment with GH.

Idiopathic GH deficiency. Of the 19 patients with idiopathic GH deficiency who were retested, 14 were confirmed as GH deficient (two partial and 12 total), with a mean (SD) interval from diagnosis to retesting of 7·4 (2·9) years. Of these, one who was initially diagnosed as totally GH deficient had a GH peak on retesting that was in the partial range

The remaining five patients produced normal GH peaks (>15 mU/l) to provocation tests at a mean (SD) interval of 7·6 (3·8) years from diagnosis (auxological details, Tables 2 and 3). Of these five patients, case 1 was thought to have familial short stature clinically, and though the first year increment on treatment was unsatisfactory he started to show a pubertal growth spurt at the end of this period, and this development combined with parental pressure led to treatment continuing until growth had ceased. Case 3 also grew an unacceptable amount in the first year but further annual velocities were enhanced with an increased dose of GH and later with puberty. Treatment with GH was thus continued. Cases 2 and 5 would have received sex steroid priming during their diagnostic studies if they had presented after 1981, but both had acceptable first year responses to GH. Case 4 was a Turner's mosaic who was on a six month trial with GH, during which time her response was favourable. GH was continued for 1·76 years until growth ceased. Using Turner's growth curve data,[19] her pretreatment height standard deviation score (SDS)

Table 3 *Mean (SD) values of various auxological variables before, during, and after treatment with growth hormone (GH) in patients with false or true idiopathic GH deficiency*

Growth variables	*Idiopathic GH deficiency group*		*p Value*
	True	*False*	
Pretreatment			
Age (years)	12 9 (3 3)	11 8 (3 7)	NS
Height SDS for chronological age	−4 7 (1 0)	−4 0 (1 2)	NS
Height SDS for bone age	−1 9 (1 4)	−1 4 (1 9)	NS
Bone age SDS	−3 5 (2 0)	−3 2 (1 7)	NS
Sitting height SDS	−5 2 (1 0)	−3 9 (1 5)	NS
Pretreatment velocity (cm/yr)	3 5 (1 8)	3 4 (1 6)	NS
First year velocity (cm/yr)	8 7 (1 8)	5 6 (0 5)	<0 01
First year increment (cm/yr)	5 2 (2 3)	2 2 (1 5)	<0 05
Post-treatment			
Height SDS for chronological age	−2 6 (1 0)	−2 6 (1 0)	NS
Height SDS for bone age	−2 4 (0 9)	−2 6 (1 0)	NS
Time on treatment	5 7 (3 0)	5 7 (3 5)	NS
Final minus predicted height (cm)	+8 4 (6 4)	+4 2 (5 4)	NS

SDS=Standard deviation score, NS=Not significant

Table 2 *Auxological data, peak growth hormone (GH) responses at diagnosis and retesting, ages before and after treatment, and year of onset of treatment in patients with false idiopathic growth hormone deficiency*

Case No	*Sex*	*Mid-parental height SDS*	*Onset of treatment*					*First year increment on treatment*	*Stopping of treatment*		
			Age (years)	*Year of onset of treatment*	*Height SDS for chronological age*	*Bone age SDS*	*Peak GH responses (mU/l)*		*Age (years)*	*Height SDS for chronological age*	*Peak GH responses (mU/l)*
1	M	−2 4	9 9	1975	−4 5	−2 9	2 0	1 7	16 3	−4 1	45
2*	M	−0 7	13 4	1979	−3 7	−3 8	4 5	2 2	18 5	−2 0	40
3	M	−0 7	6 3	1972	−2 8	−5 1	10 0	0 7	17 5	−1 5	25
4†	F	+0 7	14 2	1981	−3 0	−0 5	8 3	1 8	16 0	−2 2	27
5*	F	−1	15·1	1980	−5 7	−3 5	3 4	4 8	19 2	−3 1	44

SDS=Standard deviation score
*Primed tests would now be appropriate
†Primed tests carried out at diagnosis

was +1·33, final height SDS +1·94, and predicted final height SDS +1·74.

The characteristics of these retested patients, defined as persistent or true and transient or false idiopathic GH deficiency, are shown in Table 3. There were significant differences between the respective first year height velocities (mean (SD) 8·7 (1·8) cm/year for true idiopathic deficiency *v* 5·6 (0·5) cm/year for false idiopathic deficiency, $p<0·01$) and first year height increments (5·2 (2·3) cm/year *v* 2·2 (1·5) cm/year, respectively, $p<0·05$). The two groups could not be distinguished by auxological criteria at the time of diagnosis nor at the end of treatment

Discussion

It is not unexpected that GH deficiency seems to be permanent in distinct pathological conditions, such as craniopharyngioma or idiopathic panhypopituitarism. There has been contention, however, about the reversibility of irradiation induced GH deficiency. Griffin and Wadsworth reviewed the growth of children with malignant disease (leukaemia and solid tumours) who received cranial or craniospinal irradiation.[17] Over the three to four years of study, they found a small decrement in eventual height and no suggestion of long term impaired GH secretion and concurred with the reports of Dacou-Voutetakis *et al*[16] that the poor growth velocity in patients with leukaemia during the first year after irradiation could be due to transient GH deficiency. Shalet *et al* agreed that few children receiving CNS irradiation for leukaemia were clinically GH deficient and that their initial post-irradiation growth velocity after irradiation was poor, but they attributed this to chemotherapy, poor nutrition, and the disease itself rather than transient GH deficiency[20 21] Our results do not support the concept of transient GH deficiency when radiation induced hypophysial-pituitary damage has resulted in GH deficiency this remains and, in addition, GH secretion continues to decline for many years after the damage is inflicted.

We also suggest that the diagnosis of idiopathic GH deficiency was incorrect in 25% of patients treated in one major growth clinic over the last 14 years. This finding may seem surprising but compares favourably with other reports[22] (Burns EC, Preece MA. Personal communication. May 1986.) Such errors of categorisation are not attributable to nor avoided by baseline auxological data, which can be similar in constitutionally short children with delay in development and patients with true idiopathic GH deficiency[15 23] It is worth while repeating that the inconsistency of GH responses to pharmacological tests is an unsatisfactory diagnostic criterion. The most commonly used test, the insulin tolerance test, has a reported failure rate of 25%, where a negative response is compared with a further GH provocation test that produces normal GH concentrations,[24] thus two or more tests are routinely performed to minimise error. An additional source of error, which may have occurred in two of our patients with false idiopathic GH deficiency, is the omission of sex steroid priming before testing children in the preadolescent years. Our findings further suggest that failure to increase height velocity by 3·5 cm/year or more in the first year of treatment should lead to close scrutiny of the original diagnosis.

At a time when a widening of diagnostic categories for treatment with GH is suggested,[6] is this clinical audit of present treatment groups instructive? There seem to be three objectives of treatment with GH in the short child—namely, greater adult height, faster immediate growth, and no harmful side effects. Patients with true idiopathic GH deficiency have shown an appreciable increment in height velocity in the first year of treatment (with a mean of 5·2 cm/year) and an achieved adult height that exceeds the predicted height by a mean of +8·4 cm. Treatment of those truly deficient in GH is of benefit and we consider that this should be extrapolated to those with GH deficiency secondary to radiation damage. Assessment of the value of treatment in patients with false idiopathic GH deficiency is more difficult there was a poorer increment of height velocity in the first year, with a mean of 2·2 cm/year, but achieved adult height exceeded that predicted by a mean of +4·2 cm. It is impossible to delineate any benefit from GH in such patients, but it is reassuring that no apparent impairment of adult height was seen. We suggest that a controlled trial of treatment with GH up to adulthood in the constitutionally short with delayed development is necessary to determine whether ultimate height is increased by additional GH.

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Insulin dependent diabetes in Asians

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SUMMARY Type 1 diabetes is said to be extremely rare in children in India, where diabetes treated with insulin may be due to chronic pancreatic disease or malnutrition. To see whether typical type 1 diabetes occurred in Asian children in the United Kingdom, all known Asian children with diabetes in industrial West Yorkshire were ascertained. A total of 17 such children were studied; of these, seven were from three multiplex families and two fathers from these families had diabetes. All children were ketosis prone and developed diabetes while resident in the UK. There were significant increases in HLA-B8 and HLA-DR3 and increases in HLA-DR4 and HLA-DR3/DR4, while HLA-B15 was absent. Islet cell antibodies, either IgG or complement fixing, were present in four of 18 subjects tested, all of whom had disease of short duration. The prevalence of type 1 diabetes in Asian children aged 15 years or less in West Yorkshire was 36/100 000, assuming complete ascertainment.

It is concluded that typical type 1 diabetes may occur in Asian children and this condition may be more common in families who have migrated to the UK.

Diabetes is currently divided into two major forms.[1] Type 1 (insulin dependent) diabetes is characterised by an immune mediated slow destruction of the insulin secreting B cells of the pancreatic islets.[2] This form generally presents in childhood or early adult life, although it may occur at any age, even in the ninth decade Plasma C peptide and insulin responses to stimulation are absent or blunted[3] and patients are ketosis prone and insulin dependent The immunological basis of type 1 diabetes is signified by the presence of circulating islet cell antibodies in most subjects at the time of diagnosis. Genetic susceptibility to type 1 diabetes is strongly linked with the human leucocyte antigen (HLA) system, encoded on the short arm of chromosome 6 In white patients with diabetes there is a high prevalence of HLA-DR3 and HLA-DR4 and the uncommon heterozygous state, HLA-DR3/DR4,[4] which therefore increases the risk for the disease

In contrast, type 2 diabetes increases in prevalance with age, although it may occasionally occur in childhood.[5] Patients are often obese and have adequate insulin secretion Its pathogenesis is poorly understood; it has a strong genetic basis, although this is not HLA linked, and may result from an abnormality in the peripheral insulin receptor.[6]

The concepts underlying this classification arise from studies mostly of white west European or American subjects.

The situation pertaining to diabetes in Asians, and Indian subjects in particular, is less clear Insulin dependent diabetes presenting in childhood is said to be very rare in Asians[7] whether resident in India[8] or in the United Kingdom.[9] Earlier studies of the HLA association with insulin dependent diabetes in Asians have not shown the usual B locus antigen associations seen in west Europeans, although HLA-DR has not yet been investigated.[10]

The aim of this study, therefore, was to investigate whether typical type 1 diabetes with its HLA associations and the presence of islet cell antibodies, as occurs in west European children, is found in Asian children.

Patients and methods

All consultant paediatricians in industrial West Yorkshire (Bradford, Leeds, Huddersfield, Halifax, and Dewsbury) were asked if they had any ketosis prone, insulin dependent Asian children with diabetes aged 16 years or less under their care In addition, all relevant diabetes liaison health visitors were asked if any such children attended adult diabetic clinics. All such known children were studied. Their place of birth, age at onset of diabetes, and family history were obtained. HLA typing for A, B, and DR antigens was performed by standard microlymphocytotoxicity techniques. Islet cell antibodies in serum were sought by immunofluorescent techniques, for both 'conventional' (IgG) and complement fixing antibodies.[11] In multiplex diabetic families samples were obtained from all available family members, whereas only the proband was studied in single affected cases. All subjects and parents gave informed consent to participation in the study.

Statistical analysis was by χ^2 with Yates's correction; p values were not corrected for the number of HLA determinants tested.

Results

Seventeen Asian children with diabetes (nine boys and eight girls) were ascertained. All were born in the UK. Their mean (SD, range) age at the onset of diabetes was 7 (4, 3–16) years and mean (SD, range) duration of diabetes was 2 (1, 0·5–6) years. Three multiplex families contained seven children with diabetes, while the remaining 10 children with diabetes were isolated cases. Two of the fathers of the multiplex families had insulin requiring diabetes, and one of these also had thyroiditis; the third died of unknown causes. The geographical origins of the families of the subjects studied were Pakistan (all three multiplex families and five single cases), Kenya, although previously from north west India (three single cases), and one single case each from Kashmir and Gujarat.

The prevalence of the human leucocyte antigens that are associated with type 1 diabetes in west European subjects in the children studied is shown in the Table. HLA-B8 was significantly more common in the diabetic probands (54%) than in a control Asian population (7%) from west India ($p<0·001$), while HLA-B15 was not present in any of the subjects with diabetes, although it was present in 13% of the control population.[12] HLA-DR3 was significantly increased in the diabetic probands (85%) compared with the control population (16%) ($p<0·001$), while HLA-DR4 was also increased (38% *v* 16%), although not significantly The heterozygous HLA-DR3/DR4 combination was present in 31% of the probands, and although figures are not available for this combination in an Asian control population, this prevalence is highly likely to be significantly increased

Serum samples were available from 24 children (children with diabetes and their siblings) and four parents (with and without diabetes). Among the 18 subjects with diabetes tested (16 children and two fathers), four were positive for IgG islet cell antibodies and two for complement fixing islet cell antibodies. All those subjects positive for islet cell antibodies had a duration of diabetes of two years or less One sibling without diabetes from a multiplex diabetic family, carrying HLA-DR4, was positive for both IgG and complement fixing islet cell antibodies

The population of Asian children aged 15 or less in the area studied in 1981 was 46 977,[15] and with 17 children with diabetes in this study, the population prevalence for Asian children with diabetes is 36/100 000, assuming complete ascertainment

Discussion

This study confirms that insulin dependent diabetes with many of the characteristics of 'type 1' diabetes, as it occurs in white west European populations, can occur in Asians, who are also genetically white. The children studied had an onset of diabetes early in life and were ketosis prone There was a familial aggregation of diabetes, in that three multiplex families contained seven children with diabetes, there was a disturbance in frequencies of human leucocyte antigens, and islet cell antibodies were present in subjects with disease of short duration.

Table *Prevalence of human leucocyte antigens in the children studied compared with west European subjects*

Antigens	*Diabetic probands (n=13) (No (%))*	*Indian control population (%)**	*English children with diabetes (%)†*	*English control children (%)‡*
HLA-B8	7 (54)	7	54	32
HLA-B15	0	13	18	12
HLA-DR3	11 (85)	16	71	32
HLA-DR4	5 (38)	16	78	34
HLA-DR3/DR4	4 (31)	§	51	6

*Ten single cases and three probands (eldest child with diabetes from three multiplex families, thus excluding all related cases)
†From the control population of van Eden (n=129)[12]
‡From Cudworth and Woodrow (n=15)[13] and Wolf *et al* (n=122)[14]
§Figures not available

Our subjects tended to originate from northern India. A previous study of subjects with diabetes from that area suggested that the usual classification of diabetes into types 1 and 2 did not apply there and that 'juvenile diabetes' was extremely rare[8]

Most previous HLA studies in Asian subjects with diabetes have not examined DR antigens and have only presented results of A and B locus antigens. Only one recent study has examined HLA-DR frequencies.[16] HLA-DR3, but not HLA-DR4, was significantly increased in a group of insulin dependent north Indian patients with diabetes with onset before 40 years, although none was said to have onset in childhood. Our results showed a significant increase in HLA-B8 and HLA-DR3 and increases in HLA-DR4 and the HLA-DR3/DR4 heterozygous state, all of which are increased in white west European subjects with diabetes.[13 14] HLA-B15 (Bw62), which is also associated with type 1 diabetes in whites, was not present in any of the small number of subjects with diabetes tested. Previous studies of Asian patients with diabetes have found an increase in HLA-B8,[17 18] while a study in north India could not confirm this and found instead increases of HLA-Bw21 and HLA-B7,[19] antigens not associated with type 1 diabetes in western Europe These latter increases may have been due to technical errors in HLA typing Islet cell antibodies are present in almost all cases of type 1 diabetes at the time of diagnosis but disappear in subsequent months.[20] In accordance with this, the short duration cases of Asian children did have islet cell antigens, including the complement fixing type, which is the more important marker of recent onset diabetes It is of interest that an HLA-DR4 positive sibling without diabetes also had both IgG and complement fixing islet cell antigens and was therefore at increased risk of developing type 1 diabetes.[21 22] Islet cell antigens have previously been reported in north Indian subjects with diabetes when they were associated with coexistent autoimmunity in cases of long duration[23]

One study recently paid attention to the high prevalence of type 2 diabetes, often associated with obesity, seen in Asians in the UK.[9] In that study, Asian children with diabetes were said to be few, although the prevalence was 63/100 000 children aged 14 years or less, which was almost double that found in Yorkshire. The prevalence of diabetes among Asian children under 15 years of age in Leicester was 54/100 000 and was lower than that in non-Asian children (99/100 000), although the difference was not significant[24] Any differences between these estimates of prevalence may stem from both the small numbers involved and the degree of complete ascertainment.

It is concluded that type 1 diabetes occurs in Asian children and has the hallmarks of insulin dependence, ketosis proneness, disturbance of human leucocyte antigens, and the presence of islet cell antibodies. Whether type 1 diabetes is more common in Asian children living in the UK than it is in India is unclear, although previous reports suggest that this is the case. If so, such children may be exposed to an environmental agent in the West, which may be involved in the aetiology of diabetes that is less common in India.

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Consanguinity and fetal growth in Pakistani Moslems

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SUMMARY There is conflicting evidence about the effect of parental consanguinity on fetal growth. Previous studies have not always allowed for other factors that are known to affect birth weight, in particular, gestational age, parity, and maternal height. We have therefore studied this question in the Pakistani Moslem population in Birmingham. Babies born to parents who were first cousins were on average 80 g lighter than those born to unrelated parents, but this difference was not significant for the size of the sample studied. Nor were there any differences in the other measurements of the babies. After expressing birth weight in terms of centiles for gestational age, sex, parity, and maternal height, however, while there was no difference in the overall distribution of centiles, there were more poorly grown babies—that is, weight below the 10th centile—in the first cousin group. We conclude that parental consanguinity is associated with an increase in the number of poorly grown babies but that the overall effect on mean birth weight is small.

While some studies have shown that parental consanguinity retards intrauterine growth,[1 2] others have not found this effect.[3 4] Even in the studies that found a reduction in birth weight, it was not apparent whether the difference in birth weight was explained by differences in gestational age, parity, maternal height, etc, and not all of the studies controlled for all of these factors when comparing birth weight from different types of marriages.

In this hospital there have been increasing numbers of births to Pakistani mothers who are Moslems, followers of the Islam faith in which consanguinous marriages, particularly among first cousins, are preferred. In previous studies from this hospital it was suggested that environmental factors, such as the mother's health and nutrition in pregnancy, were more important in affecting intrauterine growth than genetic factors.[5–7]

In view of the conflicting evidence described above about the possible growth retarding effect of parental consanguinity, however, this study was designed to consider the effect of consanguinity on fetal growth after allowing for the major factors that affect intrauterine growth—for example, sex of baby, gestational age, maternal height, and parity.

Patients and methods

Babies born to Pakistani mothers between November 1982 and May 1983 at our hospital were studied. The mothers were interviewed after the birth by an Asian interpreter who obtained details of the parental relationship, their place of birth, and obstetric history. Further maternal details were ascertained (by MH or LB) from the obstetric notes. The babies were examined within 48 hours of birth (by either MH or LB): any abnormalities were noted, gestational assessment made (Dubowitz method), and length measured by neonatometer, head circumference with a paper tape measure, and skinfold thickness with Harpenden calipers at the left triceps. The birth weight from the labour ward was recorded as measured by the attendant midwife on a spring balance and all details entered onto a proforma.

The size of sample was designed to identify a difference of 100 g between first cousin and nonrelated babies as significant.[8] A total of 267 mothers were interviewed and 260 completed proformas analysed. Exclusions were due to five stillbirths, one twin pregnancy, and one incomplete form. All babies with congenital abnormalities were included.

Three groups were defined on the basis of the parental relationship—namely, first cousin or closer, more distantly related than first cousin, and unrelated.

Statistical methods. Birthweight centiles, corrected for maternal height, parity, gestational age, and sex of baby using the adjustments of Thomson *et al,* were calculated for each baby,[9 10] as were birthweight and length and head circumference centiles, corrected only for gestational age and sex using the charts of Gairdner and Pearson.[11]

Various measurements of growth and the major variables known to affect birth weight (maternal height, gestational age, sex, and parity) were compared using conventional statistical tests (for metrical variables, such as birth weight, the normal distribution test and for nominal or ordinal variables, such as sex or parity, either χ^2 test, Fisher's exact test, or Kolmogorov-Smirnoff test, as indicated in the 'Results' section).

The joint effect of the above four variables and the additional effect of consanguinity in contributing to variation in birth weight was explored using multiple regression methods.[12]

Table 1 *Weight, length, and head circumference at birth of 260 babies grouped according to parental relationships*

	Group		
	First cousin (n=122)	*Distant (n=62)*	*Unrelated (n=76)*
Birth weight (g)			
Mean (SD)	3178 (511)	3192 (533)	3258 (501)
No (%) below 10th centile			
Gairdner and Pearson†	31 (25%)*	9 (15%)	10 (13%)*
Thomson *et al*‡	21 (17%)**	4 (6%)	4 (5%)**
Length (cm)			
Mean (SD)	50 4 (2 40)	50 9 (2 78)	50 5 (1 71)
No (%) below 10th centile†	17 (14%)§	3 (5%)	5 (7%)§
Head circumference (cm)			
Mean (SD)	34 4 (1 56)	34 3 (1 82)	34 5 (1 18)
No (%) below 10th centile†	21 (17%)§	8 (13%)	9 (12%)§
Mean (SD) triceps skinfold (mm)	5 76 (1 74)	5 73 (1 48)	5 94 (1 44)

*χ^2=4 28, p<0 05 **χ^2 with Yates's correction=5 03, p<0 05
†Gairdner and Pearson for gestational age and sex[11]
‡Thompson *et al* for gestational age, sex, parity, and maternal height[9 10]
§Not significant

Results

Fetal growth. (Table 1 and Figure). Babies in the first cousin group were 80 g lighter than those in the unrelated group. This difference was far from significant (p>0·3), but there were significantly more babies below the 10th centile for birth weight in the first cousin group compared with the unrelated group (p<0·5). The babies whose weight was less than the 10th centile were then examined in more detail. Among the 31 light babies in the first cousin group, 16 were also short (length <10th centile), whereas among the 10 light babies in the unrelated group, only one was short (χ^2 with Yates's correction=3·82, p=0·05). Among the 31 light babies in the first cousin group, eight had both length and head circumference below the 10th centiles, whereas among the 10 light babies in the unrelated group, only one was symmetrically small (not significant).

Major factors affecting birth weight. (Tables 2 and 3). Details of four major factors known to affect intrauterine growth (sex, gestational age, parity, and maternal height) are shown. The first cousin group did not differ significantly in any measurement from the unrelated group.

Multiple regression analysis was performed, and the results are shown in Table 3. Variation in the four main factors accounted for less than one quarter (r^2=22·3%) of the variation in birth weight. The additional effect of consanguinity was minimal (r^2 increased by 0·6%)

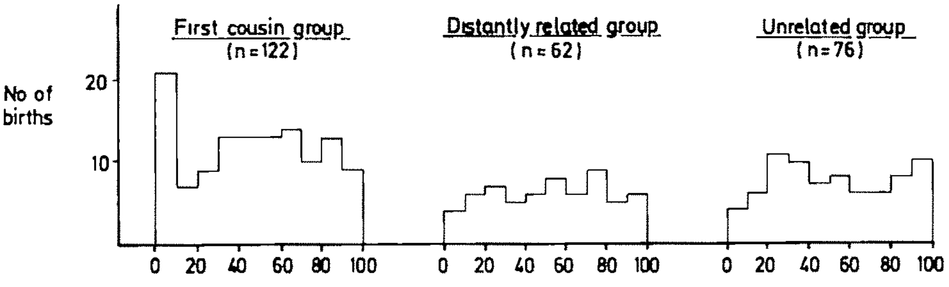

Figure *Birth weight centiles for gestation, sex, parity, and maternal height (according to reference data of Thomson* et al[9 10]*) of babies born to first cousin, more distantly related, and unrelated parents. The overall distributions of centiles were not significantly different (Kolmogorov-Smirnoff, p>0·1). The first cousin group contained significantly more babies below the 10th centile, however, (21 (17%)) than the unrelated group (4 (5%)) (χ^2 with Yates's correction=5 03, p≏0·025) but not quite significantly more than in the distantly related group (4 (6%)) (p≏0·08)*

Table 2 *Major factors affecting birth weight in 260 babies grouped according to parental relationships*

	Group		
	First cousin (n=122)	*Distant (n=62)*	*Unrelated (n=76)*
Sex (M F)	59 63	31 31	38 38
Gestational age (wks)			
Mean (SD)	39 3 (1 0)	38 8 (2 1)	39 1 (1 2)
No (%) <37 weeks	2 (2)*	6 (10)	4 (5)
Previous births			
Mean (SD)	1 9 (1 7)*	2 6 (2 0)	2 4 (2 0)
Nil (No (%))	32 (26)	10 (16)	16 (21)
1–4 (No (%))	70 (57)	38 (61)	42 (55)
>4 (No (%))	20 (16)	14 (23)	18 (24)
Maternal height (cm)			
Mean (SD)	153 2 (5 6)	154 4 (6 4)	154 0 (6 7)
No (%) <150 cm	31 (25)	12 (19)	22 (29)

*Result significantly different from that in distantly related group

Other factors affecting birth weight. There were no significant differences in maternal age, hypertension, vaginal bleeding, or anaemia between the three groups and no other maternal illness of note. Although none of the mothers smoked cigarettes, two smoked tobacco in a hookah and five took snuff. We did not enquire about alcohol in dealing with a Moslem population A small number of women (3%) had no antenatal care, and of the remainder, roughly half attended before 20 weeks and half after 20 weeks, with a similar pattern in all three groups

Consanguinity and sociological data. In the overall sample the degree of consanguinity was second cousin or closer in 62% of marriages, with 47% of marriages between first cousins, some of whom were probably even more closely related because of a first cousin marriage in the previous generation (this information was not routinely requested). There were no uncle/niece or aunt/nephew parental relationships. Relationships more distant than second cousin occurred in 9% of marriages, and in 29% the parents were unrelated

Among the 520 parents, 95% were born in Pakistan: 4% were born in other regions of the Asian or African subcontinents, with only 1% born in the United Kingdom. Unskilled factory work was the most usual occupation of the father, but only 56% of the first cousin group, 70% of the more distant than first cousin group, and 53% of the unrelated group were employed.

Congenital malformations. Table 4 shows details of congenital abnormalities of varying severity, all of which occurred within the related groups.

Table 4 *Congenital abnormalities in 260 babies grouped according to parental relationships*

Case No	*Abnormality*	*Birth weight (g)*
First cousin (n=122)		
1	Microcephaly, cataracts, small genitalia, contractures (Pena Shokeir II)	1600
2	Hypoplastic left heart	4000
3	Dextrocardia pulmonary stenosis, transposition great arteries, ventricular septal defect	2600
4	Dextrocardia, situs inversus	3180
5	Large ventricular septal defect	3920
6	Intestinal obstruction due to ectopic liver	3400
7	Right congenital dislocation of hip	2980
8	Polydactyly hands and feet	3300
Distant (n=62)		
9	Bilateral cleft lip and palate	3240
10	Ventricular septal defect and abnormal thumbs	2000
Unrelated (n=76)		
No malformations were detected		

Table 3 *Regression equations (SE) of birth weight on 'independent' variables and for related parental groups*

	Variable					*Related group*		*r² (%)**
	Constant	*Maternal height*	*Gestation*	*Sex*	*Parity*	*First cousin*	*Distant*	
Birth weight =	−4566 (1063)	+12 15 (4 69)	+150 2 (20 6)	+124 2 (57 1)	−134 4 (69 2)			22 3
Birth weight =	−4567 (1066)	+11 70 (4 70)	+153 3 (20 8)	+121 6 (57 1)	−128 1 (69 4)	−94 1 (67 5)	−30 6 (79 0)	22 9
Birth weight =	−4579 (1062)	+12 01 (4 69)	+150 6 (20 6)	+122 7 (57 1)	−133 5 (69 1)	−72 4 (62 7)		22 7

*r^2 Represents extent to which equation explains variation in birth weight, 100% represents complete explanation

The coefficients represent the birthweight increment (or decrement) in grams predicted from a unit increment in each 'explanatory' variable For example, in the first equation, each additional centimetre of maternal height would be associated with a 12 g increase in birth weight The sex 'variable' reflects the increment for a boy compared with a girl The parity variable is the decrement for the first born child compared with subsequent children Similarly, the 'first cousin' and 'distant' measurements show the decrement in birth weight if the parents are in one of these categories compared with being unrelated

Table 5 *Comparison of studies of effect of parental consanguinity on fetal growth*

Study	*Country (population studied)*	*Numbers*			*Birth weight (g)*					*Other factors affecting birth weight allowed for in statistical analysis*	*Other body measurements*
		Total	*Consanguineous*	*Unrelated*	*Mean consanguineous*	*Mean unrelated*	*Difference (consanguineous-unrelated)*	*Significance of difference*	*Weight for gestational age, parity, sex, and maternal height (% <10th centile)*		
Sibert[1]	India (Tamil Nadu)	322	126	196	2731	2834	−103	p<0.01		Gestational age—term babies only included	Length, head circumference, skinfold thickness
			UN 52		UN 2650						
			C1 61		C1 2794						
			C2 13								
Morton[2]	Japan	75180	C1 2928	70088	C1 3046	3074	−28			Gestational age, parity, city	
			C2 2144								
Schork[3]	Japan	2314	230	2084	3099	3091	+8	NS		Parity, sex, maternal age, paternal age, month of birth	Head circumference, chest girth
Rao[4]	India (Tamil Nadu)	14243	Rural								Length, head circumference, chest girth
			3889	4449	2740	2772	−32	NS			
			UN 1308								
			C1 1991								
			C2 590								
			Urban								
			1654	4251	2883	2867	+16	NS			
			UN 371								
			C1 989								
			C2 294								
Slatis[13]	United States (white)	108	63	45	3247	3352	−105	NS			
Paddaiah[14]	India (Andhra Pradesh)	4823	1821	3002	2820	2880	−60	p<0.001		Sex, socioeconomic state	Length, head circumference, chest girth, calf girth
This study	United Kingdom (Pakistani Moslems)	260	C1 122	76	C1 3178	3258	−80	NS	C1 (17)*	Gestational age, sex, parity, maternal height	Length, head circumference, skinfold thickness
			C2 62		C2 3192		−66	NS	C2 (6)		
									Unrelated (5)		

*p<0.05
NS=Not significant
C1=first cousins, C2=more distant than first cousin, UN=uncle/niece

Discussion

Table 5 summarises the results of this and previous studies.[1–4] [13] [14] There is conflicting evidence for the effect of parental consanguinity on fetal growth, but in almost all studies the mean birth weight of the related groups was lower than that of the unrelated groups. In this study, although a reduction of 80 g was found in the first cousin group compared with the unrelated group, the difference was not significant for the size of the sample studied, which was chosen to detect a difference in birth weight of 100 g or more.

Two different statistical techniques found consanguinity to have no significant effect on birth weight after allowing for gestational age, sex, parity, and maternal height—that is, the overall distributions of birthweight centiles were no different and multiple regression found only a minimal effect There were significantly more babies in the first cousin group, however, who were below the 10th centile for birth weight. Of these light babies in the first cousin group, half were also short (length below the 10th centile) and one quarter uniformly small (length and head circumference below the 10th centile). Proportionately fewer of the babies less than 10th centile in the other groups were uniformally small, but the total numbers were small and not significant.

If parental consanguinity does have a growth retarding effect it is therefore not clear whether it acts by depressing all growth variables from an early stage or whether weight gain is more affected at a later stage in pregnancy, possibly as a result of poorer placental function. Growth retardation may also be part of a recognised recessively inherited condition (Table 4, case 1), but this mechanism is likely to have little overall effect on the mean birth weight. While the excess of babies with congenital abnormalities of varying severity in the related groups was striking, this prospective study was not designed to investigate this controversial question,[4] [15] and further studies are awaited.

Although the validity of using the adjustments of Thomson *et al* on an Asian population has not been established, the same criteria for adjustment was applied to all groups and indeed the centile distribution of our unrelated group was close to that of their reference population Perhaps this 'significant finding' is a mere statistical artefact, reflecting the arbitrary nature of the 10th centile cut off point. Nevertheless, this cut off point is in wide clinical use to indicate babies who may require special attention in the newborn period.

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Vasoactivity of the major intracranial arteries in newborn infants

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SUMMARY Blood flow to the head and arms was measured by a new volumetric Doppler technique in 30 preterm infants and 10 full term infants. At least 80% of this blood flow is considered to perfuse the brain. At the same time mean blood velocity in the middle and anterior cerebral arteries was measured by Duplex Doppler scanning. While blood flow to the head and arms remained substantially constant in both groups over the first 48 hours of life (60 ml/100 g brain weight/min), blood velocity doubled in both cerebral arteries in the preterm group. The term infants had higher blood velocities in both arteries at all times, but the velocities also increased over 48 hours, although to a lesser extent than in the preterm group. These findings imply that the major intracranial arteries are themselves vasoactive, being dilated at birth and subsequently constricting, possibly as an autoregulatory response to rising arterial blood pressure. While vasodilated, the cerebral arteries will be less efficient at damping pressure transients, placing preterm infants at particular risk of periventricular haemorrhage during the early hours of life. The implications for possible approaches to the prevention of cerebral haemorrhage are discussed.

Despite extensive investigation, the physiological and pathological mechanisms underlying both cerebral haemorrhage and ischaemia in the preterm newborn infant remain controversial. The common observation of a high incidence of periventricular haemorrhage during the first 48 to 72 hours of life[1 2] and the relative rarity thereafter, irrespective of the severity of later illness, has led to the hypothesis that susceptibility to haemorrhage and possibly cerebral ischaemia is related to the process of cardiovascular adaptation to extrauterine life. In this study we investigated the dynamics of the cerebral circulation in both full term and preterm infants during the first 48 hours of life.

Doppler techniques may be used to measure the velocity of blood within the anterior and middle cerebral arteries through either the anterior fontanelle or the thin bone of the newborn infant's skull.[3 4] Although under experimental conditions and in animal models mean velocity in the anterior cerebral arteries has been shown to correlate with cerebral blood flow, the use of measurements of cerebral artery velocity to predict cerebral perfusion presupposes that these arteries do not themselves change in calibre. Physiological studies in mature animals have suggested that the arteries as proximal as the circle of Willis have a capability to dilate and constrict, particularly in response to changes in perfusion pressure.[5–8] A new volumetric Doppler technique has therefore been devised that makes no assumptions about the vasomotor properties of the arteries supplying the brain.

Patients and methods

Study populations. We studied two groups of infants.

The preterm group comprised 30 infants born at the Bristol Maternity Hospital between June 1985 and January 1986 with a gestation of 33 weeks or less (range 24–32 weeks, median 30 weeks), excluding those with congenital malformation. Their birth weights ranged from 760 to 2140 g, with a median of 1430 g. Their clinical characteristics are summarised in Table 1.

The term group comprised 10 infants with a gestation of 37 weeks or more (range 38–41 weeks, median 40 weeks) born during the same period and who had no perinatal problems. Their birth weights ranged from 2730 to 3960 g, with a median of 3275 g.

Table 1 *Clinical characteristics of preterm study group (n=30)*

Sex (M F)	13 17
Reason for delivery	
Spontaneous preterm labour	18
Antepartum haemorrhage	5
Prolonged rupture of membranes (complicated)	6
Hypertension	1
Delivery (vaginal caesarean section)	18 12
Singletons twins	22 8
Respiratory distress syndrome	16
Outcome	
Periventricular haemorrhage (real time ultrasound)	4
'Flares' and/or periventricular leucomalacia (real time ultrasound)	5
Survival to discharge from hospital	29

Principles and instrumentation. In the newborn infant blood leaving the left ventricle is distributed by way of the aortic arch to three major vascular territories—the head and arms, the pulmonary circulation through the patent ductus arteriosus, and subdiaphragmatic structures. Blood velocity within the aorta may be calculated from the Doppler shift in ultrasound frequency returned by moving blood cells according to the formula:

Velocity=frequency shift × c / 2fcosA

where c is the speed of ultrasound in tissue (1500 cm/sec), f is the frequency of ultrasound (5 MHz in this study), and A is the Doppler angle.

The vessel cross-sectional area may be calculated from M mode measurement of its diameter, assuming a circular section, and the volume flow obtained by multiplication of area and mean velocity The technique has been widely described in both adult and paediatric publications for the measurement of cardiac output [9 10] If flow is measured before and after the origin of the great vessels leaving the aortic arch subtraction will leave that portion of blood flow that supplies the head and arms. In the adult about 77% of this blood perfuses the brain. (Skidmore R Unpublished observations. See appendix.) In the newborn infant, particularly the preterm infant, where the brain is large compared with the body, this proportion will be even higher (at least 80%) and so this measurement is likely to be a good indicator of cerebral perfusion Brain weight may be estimated from the head circumference according to the method of Dobbing and Sands,[12] which allows blood flow to be standardised between patients.

Doppler signals from the ascending aorta were obtained in the substernal four chamber view where an oblique Doppler angle allows more even sampling across the vessel diameter than is possible using the suprasternal approach. Signals from the preductal descending aorta were obtained in the long axis view from the suprasternal or left supraclavicular window

The instrumentation used was a Duplex scanner (ATL Mk 600, ATL, Bellevue, Washington State) with 5 MHz Doppler flowmeter directly interfaced to a microcomputer (Apple IIe). The Duplex system uses the real time image for identification of the vessel, precise placement of the discrete Doppler sample volume, and measurement of the Doppler angle. The digitally encoded Doppler spectrum is stored in computer memory. Here noise is removed by thresholding before computing mean and maximum frequency shift contours, which are stored on disc and used for calculation of flow variables. The system allows about 3·5 seconds of Doppler signal to be collected, corresponding to four to eight cardiac cycles.

Errors in Doppler assessment of volume flow may be both random and systematic. The random errors resulting from inaccuracy in determination of the vessel size and Doppler angle may be reduced by taking the mean of several measurements at each site. In most cases a minimum of four observations were made. Systematic errors largely arise from preferential sampling of the central stream velocity in larger arteries and have been minimised by laboratory calibration of the system over a range of vessel diameters using a pulsatile flow rig

Measurements of the *velocities* in the anterior and middle cerebral arteries were made with a similar technique, using a transfontanelle approach in the former case and a temporal approach for the latter, a near zero Doppler angle being achieved in each case Arterial blood pressure in the preterm group was measured non-invasively using the oscillometric method (Sentry Automated Blood Pressure Monitor, Automated Screening Devices Inc, California), with the cuff placed whenever possible on the right arm Doppler and blood pressure measurements were made at fixed intervals after birth—between 1 and 2 hours and at 12, 24, and 48 hours. Infants in the preterm group also had measurements made at 6 hours

The results were analysed using paired and unpaired *t* tests (two tailed) for velocity and blood pressure data and Wilcoxon signed ranks, matched pairs, or Mann-Whitney U tests as appropriate for volumetric data (also two tailed)

Informed parental consent was obtained for this study.

Results

Velocity. In both the middle and anterior cerebral arteries of the preterm infants there was a progressive increase in velocity over the first 48 hours of life

(Figures 1 and 2); at 48 hours the velocities were about double those shortly after birth ($p<0{\cdot}001$ for each artery). A similar but less pronouced change was seen in the term infants (significantly only for the anterior cerebral artery, $p<0{\cdot}01$) At each age studied the velocities in the term infants were significantly higher than in the preterm infants

Blood flow to head and arms. In contrast there were no significant differences in blood flow to head and arms per 100 g brain weight over this period in either the preterm or term groups (Table 2), but flow per unit mass was similar in the two groups. On subtracting an estimated 20% from these values to compensate for blood perfusing tissues other than the brain, our mean estimate of cerebral blood flow for both groups was 46 ml/100 g brain weight /min for the full term group and 51 ml/100 g brain weight/min for the preterm group.

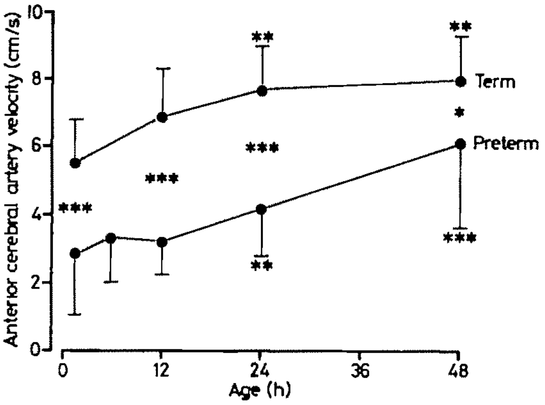

Fig 1 *Mean (SD) velocities in the anterior cerebral artery in the two groups. There were significant differences between term and preterm infants at all ages and significant increases in velocity from initial recordings in both term and preterm infants by 24 hours of age*

*p<0·05 **p<0·01 ***p<0·001

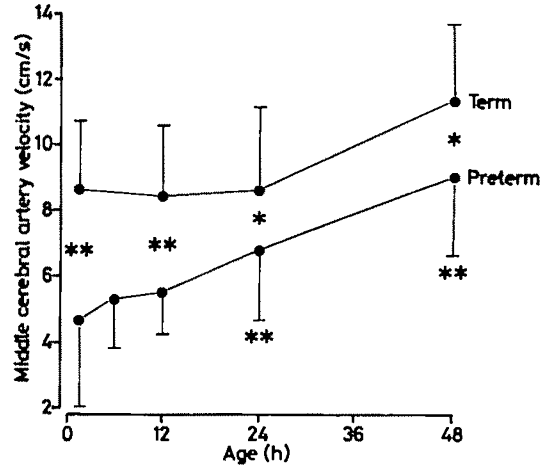

Fig. 2 *Mean (SD) velocities in the middle cerebral artery in the two groups There were significant differences between term and preterm infants at all ages and significant increases in velocity from initial recordings in the preterm infants by 24 hours of age.*

*p<0·05 **p<0·001

Arterial blood pressure. Mean arterial blood pressure increased progressively in the preterm infants (Table 2). The differences were significant at 24 and 48 hours ($p<0{\cdot}01$).

Discussion

The values of 46–51 ml/100 g brain weight/min were well within the wide range of values for cerebral blood flow measured using other techniques,[13] and the similar values obtained in both term and preterm infants lends credence to this Doppler method. The

Table 2 *Blood flow to head and arms (ml/100 g brain weight) and arterial blood pressure (mm Hg) over the first 48 hours of life (insufficient blood pressure data on term infants)*

Age (hours)	*Full term infants*				*Preterm infants*						
	Flow to head and arms			*(n=)*	*Flow to head and arms*			*Mean blood pressure*			*(n=)*
	Mean	*(SD)*	*95% Confidence limits*		*Mean*	*(SD)*	*95% Confidence limits*	*Mean*	*(SD)*	*95% Confidence limits*	
1·5	57·0	(21·5)	41–73	(10)	62·0	(37·2)	48–76	40·4	(8·0)	37–44	(29)
6·0	—	—	—		63·4	(36·4)	50–77	43·4	(9·1)	40–47	(29)
12·0	59·1	(12·5)	50–68	(10)	60·7	(32·2)	49–72	43·6	(8·6)	40–47	(30)
24·0	59·5	(13·6)	49–70	(10)	69·6	(34·1)	57–83	45·9	(7·2)	43–49	(28)
48·0	55·6	(16·6)	43–68	(10)	62·6	(28·1)	52–73	49·4	(11·0)	45–54	(28)

constancy of cerebral blood flow in both groups of infants over a period during which arterial blood pressure and presumably also cerebral perfusion pressure is rising (Table 2)[11] suggests that autoregulation was intact at least for most of the infants studied.

The anterior and middle cerebral arteries between them supply blood to a large proportion of the brain and so velocities in these two arteries may be assumed to be representative of the velocities in all major cerebral arteries. As blood flow is the product of velocity and cross-sectional area the likely explanation of the constant cerebral blood flow with increasing velocities is that the major arteries have altered calibre, being dilated at birth but progressively constricting over the next 48 hours. The ratio between flow and mean cerebral artery velocity provides a measure of cerebral artery area, which may be seen to decrease over time (Fig. 3).

Physiological studies of the cerebral circulation in mature animals may provide an explanation for these findings. By measuring pressure gradients across various segments of the cerebral arterial system during hypo- and hypertension, several workers have shown that the major cerebral arteries are responsible for a large part of cerebral autoregulation, while 'chemical' control of cerebral perfusion operates more peripherally.[5-8] Arterial blood pressure is low at birth and progressively increased in both preterm (Table 2) and term infants.[11] We may postulate that the progressive reduction in arterial calibre may be part of the autoregulatory response to these perfusion pressure changes. Histological examination of the cerebral arteries show that they have an ample muscle layer to accomplish the calibre change that we have described, but whether the mechanism of the change is humoral, neurologic, or myogenic remains speculative.

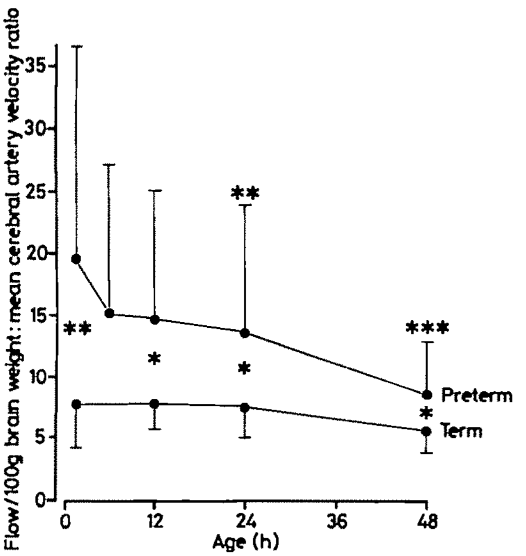

Fig 3 *Mean (SD) standardised flow velocity ratios in the two groups, showing that preterm infants were significantly more cerebrally vasodilated than term infants at all ages but that they became more vasoconstricted with age (significant from 24 hours of age).*

*$p<0.05$, **$p<0.01$, ***$p<0.001$

Cerebral artery velocities were higher in the term infants, while apparent cerebral blood flow was similar in both groups. The ratio between flow and velocity—that is, cerebral vessel area—shows not only a progressive reduction in calibre with time but also a markedly increased vessel calibre per unit brain weight in the preterm infants (Fig. 3). This is to be expected as arterial blood pressure is higher in term than in preterm infants, while perfusion per unit brain mass is similar.

Volpe and his group have advanced the hypothesis that periventricular haemorrhage occurs with transient surges in blood pressure and have shown that an unstable pattern of blood pressure is characteristic of infants with respiratory disease, particularly those who do not synchronise with their ventilators.[14 15] These surges are more likely to be transmitted to the delicate capillary beds as the degree of dilatation of the large cerebral arteries becomes greater. In other words, the risk is greater the more preterm and the younger the infant. This is in accord with observed fact.[1] Thus the susceptibility of these infants to haemorrhage may be not so much due to a *failure* of autoregulation, as has been widely suggested, but rather a consequence of the mechanism by which autoregulation is achieved. Similarly, the very preterm and the very young infant with maximal cerebral vasodilatation might be at or to the left of the autoregulatory portion of the preterm pressure/cerebral blood flow curve and thus be simultaneously at high risk of cerebral ischaemia as well as haemorrhage.

These observations may also have therapeutic implications. If the cause of cerebral arterial vasodilatation is hypotension then methods of supporting the circulation during the early hours of life may be effective in lowering the risk not only of cerebral ischaemia but also of haemorrhage. The ready improvement in peripheral perfusion and arterial blood pressure attendant on colloid infusion in many sick preterm infants suggests that their relative hypotension is secondary to hypovolaemia. The report of a reduced incidence of periventricular haemorrhage after routine administration of plasma to preterm infants[16] is of interest in this respect.

More work is required to determine the effects of circulatory support on both cardiac function and on the cerebral vasculature. Doppler ultrasound offers an apparently safe and convenient method for continuing the investigation of the neonatal circulation.

Appendix

Doppler ultrasound flow measurements in the adult neck (ml/min)

Brachiocephalic trunc	700	leaving aortic arch 700+500+200 =1400
Left common carotid artery	500	
Left subclavian trunc	200	
Internal carotid arteries 380 each		to brain 2(380+160)=1080
Vertebral arteries 160 each		

Approximate percentage flow to brain = 1080/1400×100 = 77%.

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Cardiovascular effects of tolazoline and ranitidine

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SUMMARY The cardiovascular effects of ranitidine were studied in 12 children with congenital heart disease who had been given tolazoline as a pulmonary vasodilator. Ranitidine was given as prophylaxis against gastrointestinal haemorrhage induced by tolazoline. Tolazoline 1–2 mg/kg caused significant falls in pulmonary and systemic vascular resistances and a rise in heart rate. After intravenous administration of ranitidine 3 mg/kg both resistances rose again and neither resistance then differed significantly from baseline levels. Heart rate also fell and the final heart rate was significantly below baseline levels. We conclude that there may be H_2 receptors within the pulmonary and systemic circulations and that tolazoline may mediate some of its effects through these H_2 receptors rather than by alpha adrenergic receptor blockade. The safety of H_2 blockade in children, particularly those with pulmonary hypertension, needs further investigation.

Tolazoline is an alpha adrenergic blocking agent that has been widely used as a pulmonary vasodilator, particularly in babies and small children.[1-3] Indications for its use include preoperative assessment of pulmonary vascular damage in children with congenital heart disease,[1] management of postoperative pulmonary hypertensive crisis,[2] and pulmonary hypertension secondary to pulmonary parenchymal disorders.[3] Although effective, tolazoline is associated with a high incidence of complications, including systemic hypotension, renal failure, and acute upper gastrointestinal haemorrhage, this last effect being presumably related to its H_2 agonist properties.[3] It would be logical to try to prevent this potentially life threatening side effect by the prophylactic administration of an H_2 blocker, such as ranitidine or cimetidine

The specific H_2 antagonist ranitidine has been used to treat many children with peptic ulcer, short bowel syndrome, and other gastrointestinal conditions.[4] It has also been administered to more than 2400 women in labour as prophylaxis against gastric aspiration.[5] There were no ill effects on the babies, despite equal ranitidine concentrations in umbilical cord and maternal blood when it was given intravenously.[5] On this basis, ranitidine seems to be a safe prophylaxis against upper gastrointestinal bleeding induced by tolazoline. It has been suggested, however, that tolazoline may affect the pulmonary circulation through histamine receptors [6] The less selective H_2 blocker cimetidine may antagonise the pulmonary vasodilator effect of tolazoline.[2]

The aim of this study was to assess the effects of tolazoline and ranitidine on the pulmonary and systemic circulation in children with pulmonary vascular disease secondary to congenital heart disease who required diagnostic or therapeutic administration of pulmonary vasodilators.

Patients and methods

Patients. Details of the 12 children studied are given in the Table. Case 1 was studied in the intensive care unit to optimise pulmonary vasodilator treatment, and the other children were studied in the cardiac catheterisation laboratory as part of the assessment of pulmonary vascular disease. In no child was the arterial duct patent at the time of study Cases 2, 4, and 10 had undergone palliative mustard operations before the study Informed consent was obtained from the parents in all cases before the procedure, and the protocol had been approved by the ethics committee of our hospital.

Methods. Full details of the measurement techniques have been published elsewhere.[7] [8] In summary, the children were anaesthetised for the duration of the study using intravenous etomidate. They were paralysed and ventilated through a close fitting endotracheal tube. Stability and adequacy of ventilation throughout the study were checked by

Table *Details of patients studied, in descending order of baseline pulmonary vascular resistance*

Case No	Age (yrs)	Diagnosis	Pulmonary vascular resistance (mm Hg/l/min/m²)		Pulmonary blood flow (l/min/m²)		Pulmonary artery pressure (mm Hg)	
			Baseline	Best	Baseline	Best	Baseline	Best
1	1	Endomyocardial fibroelastosis	25·00	14·10	2·95	3·55	88	59
2	7	Transposition of the great arteries, ventricular septal defect	16·79	16·39	3·46	3·91	63	63
3	5	Down's syndrome, venticular septal defect, patent foramen ovale	9·57	8·74	5·23	6·29	56	53
4	4	Transposition of the great arteries	11·80	8·50	2·60	4·40	38	38
5	4	Atrioventricular septal defect, Down's syndrome	9·37	8·36	5·79	6·84	62	62
6	0·8	Patent arterial duct, bronchopulmonary dysplasia	8·30	7·35	2·95	3·60	30	30
7	2	Atrioventricular septal defect, pulmonary artery banded	7·90	6·70	2·80	2·80	25	18
8	4	Aortopulmonary window	6·63	4·68	9·50	11·54	68	59
9	4	Patent arterial duct, ventricular septal defect, parachute mitral valve	6·08	4·46	4·85	5·00	55	44
10	3	Transposition of the great arteries, pulmonary artery banded	5·30	5·10	2·90	3·60	24	24
11	4	Double outlet right ventricle, patent arterial duct	3·87	3·54	9·68	9·68	40	31
12	6	Ventricular septal defect, patent arterial duct, coarctation	3·80	3·40	4·40	4·40	27	23

monitoring end tidal gases using remote respiratory mass spectrometry. The children were initially ventilated with air. Catheters filled with fluid were introduced percutaneously into the femoral artery and vein and positioned in the aorta and pulmonary artery, respectively. Any necessary diagnostic procedures, including measurement of left and right atrial pressures but excluding angiography, were performed before the measurements were made.

When a steady respiratory state had been attained, as defined by an end tidal carbon dioxide tension stable to within 0·25 kPa over several minutes,[8] measurements of aortic and pulmonary artery pressure and pulmonary and (where possible) systemic blood flow were made. Flow was measured by the direct Fick principle, oxygen consumption being measured by remote respiratory mass spectrometry[7 8] and blood oxygen contents calculated using the subroutine of Kelman.[9] The respiratory exchange ratio was measured on air and used in the equations to calculate oxygen consumption on 100% oxygen, as described elsewhere [10]

After the measurements on air the children were ventilated with 100% oxygen. Comparability of ventilation and adequacy of nitrogen washout were checked by monitoring the expired gases. After 10 minutes on 100% oxygen, by which time nitrogen washout was always complete, all measurements were repeated. The patients breathed 100% oxygen for the rest of the study. Tolazoline 1 mg/kg was then given through the pulmonary artery catheter by bolus injection and all measurements were repeated five and 10 minutes after the drug had been given. Provided that mean aortic pressure had not fallen by more than 20 mm Hg, a further 1 mg/kg of tolazoline was then given and the measurements repeated. Finally, ranitidine 3 mg/kg was administered 10 minutes after the final dose of tolazoline by slow injection over five minutes through a peripheral venous cannula. The final measurements were made five and 10 minutes after the end of the injection of ranitidine.

Results

Measurements were made five and 10 minutes after each dose of each drug. There was no significant difference for any variable between the five and 10 minute measurements after any dose of either drug (Student's paired *t* test). Analysis of the drug effects was therefore performed on the mean of the two measurements for each drug The effects of tolazoline and ranitidine on the pulmonary and systemic circulations and heart rate are summarised in the Table and the Figure. For statistical analysis the results have been expressed as percentages of the values on 100% oxygen before administration of the drugs because of the wide variation in baseline measurements between individuals. Paired *t* tests have been used throughout.

The first dose of tolazoline 1 mg/kg resulted in a fall in pulmonary vascular resistance (PVR) (mean (SEM) fall 10·0 (3·6)%, $p<0{\cdot}05$). A second bolus of tolazoline 1 mg/kg was given to 10 children, but

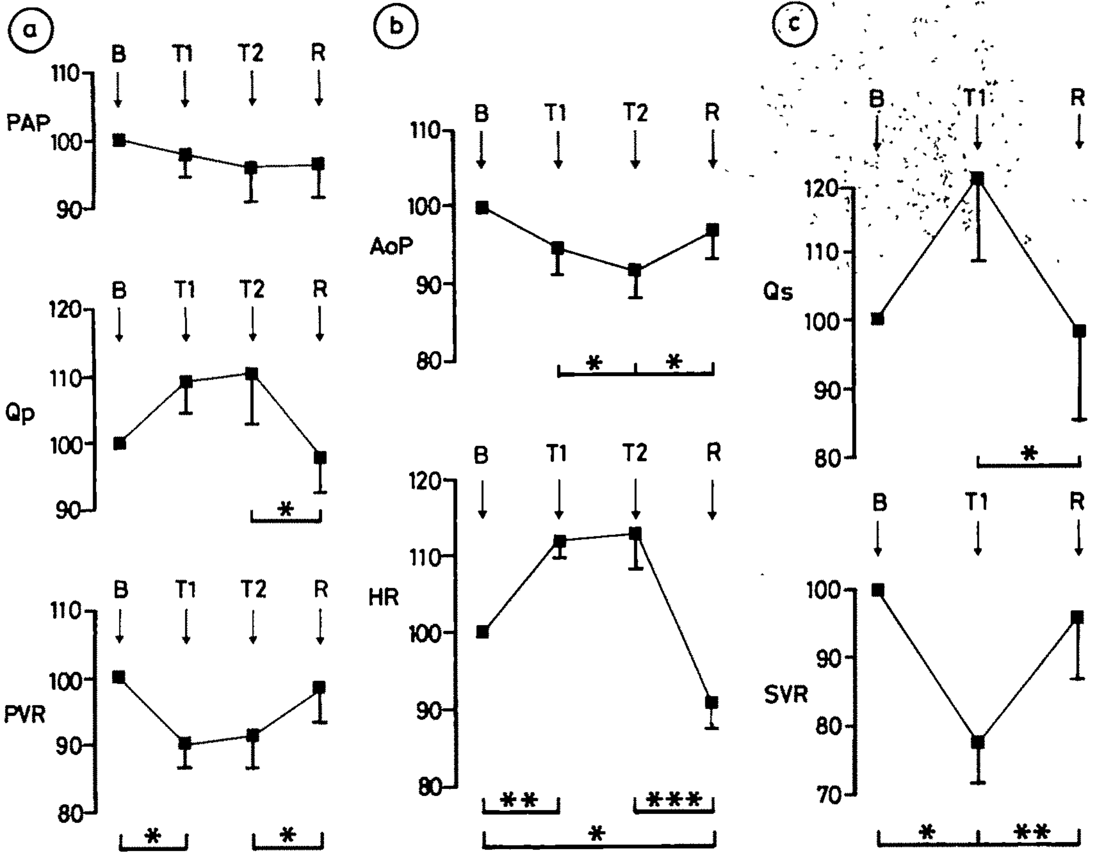

Figure *Effects of tolazoline and ranitidine on the pulmonary and systemic circulations and heart rates B=baseline, T1=first dose of tolazoline, T2=second dose of tolazoline, R=after ranitidine. All effects are expressed as per cent change over baseline (100% oxygen)*

(a) Effects on pulmonary artery pressure (PAP), pulmonary blood flow (Qp), and pulmonary vascular resistance (PVR),

(b) Effects on aortic pressure (AoP) and heart rate (HR),

(c) Effects on systemic blood flow (Qs) and systemic vascular resistance (SVR) Note only data for the first dose of tolazoline is available, and this figure is based on data for five patients

$^*p<0\cdot05$, $^{**}p<0\cdot01$, $^{***}p<0\cdot001$

there was no significant additional fall in PVR for the group as a whole. Two children (cases 7 and 8) showed a further fall in PVR, however, greater than 10%. Infusion of ranitidine reversed the fall in PVR previously produced by the tolazoline injections (mean (SEM) rise 8·7 (3·5)%, $p<0\cdot05$), so that the final PVR, after both tolazoline and ranitidine had been given, did not differ significantly from that on 100% oxygen alone. Changes in PVR were due mainly to changes in pulmonary blood flow; pulmonary artery pressure did not change significantly at any time, in agreement with previous studies.[8 10]

Similar effects were found on the systemic circulation. The first dose of tolazoline caused a fall in mean aortic pressure (mean (SEM) fall 5·4 (3·1)%, p=NS) and the second dose resulted in more pronounced hypotension (a further fall of 6·3 (2·4)%, $p<0\cdot05$). This effect was also reversed by ranitidine (mean (SEM) rise in aortic pressure 7·4 (2·9)%, $p<0\cdot05$), and the aortic pressure after administration of ranitidine did not differ significantly from that on 100% oxygen (baseline). We were able to measure systemic blood flow and systemic vascular resistance in five children in whom there were no intracardiac shunts at the time of study. There were sufficient data to analyse only the effects of the first dose of tolazoline. Systemic blood flow rose in four of the five children, but the result was not significant. When ranitidine was given systemic blood flow fell (mean (SEM) fall 21·1 (9·8)%, p<0·01) and returned to baseline rates Similarly, systemic vascular resistance fell when tolazoline was given (mean (SEM) fall 22·8 (12·9)%, p<0·01) and rose to baseline levels after administration of ranitidine (mean (SEM) rise 21·8 (9·4)%, p<0·01). The ratio of pulmonary to systemic vascular resistance rose significantly after tolazoline (mean (SEM) rise 15·8, (5·3)%, p<0·05) and fell to baseline levels after ranitidine (mean (SEM) fall 18·7 (5·1)%, p<0·05).

The heart rate results were different. The first dose of tolazoline caused tachycardia (mean (SEM) rise in heart rate 12·4 (2·5)%, p<0·001), but there was no significant additional increase in heart rate after the second tolazoline bolus. When ranitidine was given heart rate fell (mean (SEM) fall 19·0 (5·1)%, p<0·01). After the administration of ranitidine heart rate was significantly lower than on 100% oxygen alone (mean (SEM) difference 9·2 (3·1)%, p<0·05), which contrasted with the other haemodynamic measurements.

Discussion

The major finding of this study was that H_2 receptor blockade in children may have important cardiovascular effects. Intravenous ranitidine completely reversed systemic and pulmonary vasodilation induced by tolazoline and, in addition to reversing the tachycardia associated with tolazoline, seemed to have a direct negative chronotropic effect on the heart. The accuracy of the measurements, the assumptions that have had to be made, and the wider importance of these results are discussed below

Cardiac output was measured by the direct Fick principle. Oxygen consumption was measured by remote respiratory mass spectrometry.[7, 8] This method has been compared with the standard technique using a gas meter and Douglas bag collection and the systematic error found to be equal to or less than 0·6%, with the standard deviation of single estimates plus or minus 3%.[7] Blood gas analysis was performed on an automatic pH and blood gas electrode system (Corning 165) Studies with blood tonometered with physiological concentrations of oxygen and carbon dioxide have shown that this system measures blood gas tensions to an accuracy of 0·27 kPa. The effects of delays up to 20 minutes before analysing the blood samples have been shown to be negligible.[8]

In the presence of intracardiac right to left shunts (seven patients) the use of an aortic rather than a pulmonary vein sample in the Fick equation would result in overestimation of pulmonary blood flow. We therefore used the alveolar air equation to predict the oxygen content of pulmonary end capillary blood, substituting this for pulmonary venous blood in the Fick equation, thus measuring effective pulmonary blood flow. In the presence of parenchymal lung disease this approximation would be inaccurate None of these seven patients, however, had any clinical or radiological evidence of lung disease. The alternative of repeated manipulations of the right heart catheter from the pulmonary artery into the pulmonary veins through any interatrial communication for each measurement would have prolonged the procedure unacceptably. In three patients we compared predicted pulmonary end capillary blood oxygen content with pulmonary vein blood oxygen content on five occasions. Agreement was good (mean (SE) difference 0·49 (0·17) mg/dl). In three further patients aortic blood saturation was greater than 99% on 100% oxygen, despite angiographic evidence of right to left intracardiac shunting. This suggests that there were no large areas of ventilation to perfusion mismatch in at least six of the children in whom the alveolar air equation was used (cases 3, 5, and 7–11) Further discussion of the use of the alveolar air equation under these circumstances can be found elsewhere.[10]

It is important to keep the duration of general anaesthesia as short as possible and this imposed some constraints on the timing of measurements. The circulatory effects of tolazoline have been reported to reach a plateau within five to 10 minutes of a bolus injection and to remain unchanged for four to six hours[2, 11] There was no significant difference between the measurements five and 10 minutes after the bolus, and so we assumed that a plateau had been reached, and the mean of the two measurements was used for comparisons. Ideally, we would have checked this assumption by making further measurements before giving ranitidine There is no information about the speed of onset of any cardiovascular effects of ranitidine in children, and we would have liked to have examined the time course of its effects. Further extending the duration of the catheterisation and the general anaesthetic, however, could not be justified and so we were unable to determine the maximum circulatory response to ranitidine or its duration of action. From our measurements it seemed that the effects may have reached a plateau, but there is no conclusive proof of this.

This study has confirmed that tolazoline is a pulmonary vasodilator that also has pronounced systemic effects, notably tachycardia and hypotension. In the past these effects have generally been attributed to blockade of cardiovascular alpha adrenergic receptors,[1-3] although there have been suggestions that histamine receptors are important.[6] Systemic hypotension limits the doses of tolazoline that can be given safely. Tolazoline has many other side effects, including gastrointestinal bleeding, presumably related to its H_2 agonist properties.[2] It seemed rational to give an H_2 blocking agent to prevent this potentially life threatening side effect Ranitidine was chosen because it is reported to have only H_2 antagonist properties, whereas cimetidine also has gonadotrophic and other effects.[12] When ranitidine was infused intravenously, however, the vasodilator effects seen after tolazoline were totally abolished five and 10 minutes after the end of the infusion, suggesting that the cardiovascular effects of tolazoline may be mediated by H_2 receptors Heart rate after ranitidine was significantly lower than baseline, suggesting that ranitidine has a direct negative chronotropic effect.

Ranitidine acted as a systemic and pulmonary vasoconstrictor. At the time of its administration the children were exposed to two pulmonary vasodilators, 100% oxygen and tolazoline. The effects of ranitidine on the pulmonary circulation could therefore be a result of blockade of either or both vasodilators or by an entirely independent mechanism. We cannot distinguish between these possibilities, but the most probable explanation is that ranitidine blocked the effects of tolazoline on the pulmonary vasculature. Experimental work on animals suggests that histamine is not involved in the modulation of the response of the pulmonary circulation to changes in alveolar oxygen tension[13] Other workers have suggested that the H_2 agonist effects of tolazoline may be more important than the alpha adrenergic antagonist activity in the pulmonary circulation,[6] and our results support this. A direct effect of ranitidine on pulmonary vascular resistance cannot be excluded as it was not given to patients who had not been pretreated with tolazoline. Ranitidine could also have interacted with receptors other than H_2 receptors, but no such effects have ever been reported.

Studies on the circulatory effects of histamine and H_1 and H_2 receptor blockade have produced conflicting results, suggesting that there may be age and species related differences in effects When newborn lambs have been made hypoxic to raise the PVR histamine infusions have caused pulmonary vasodilation and, at larger doses, systemic vasodilation.[13] The pulmonary effects were mediated by both H_1 and H_2 receptors. Similar findings have been reported in fetal lambs,[14] calves,[15] and adult cats.[16] In adult animals histamine may constrict or dilate pulmonary arteries.[13-16]

Although histamine causes a fall in pulmonary and systemic vascular resistances in normal adult humans,[17] it has been shown to cause contraction of isolated strips of human pulmonary artery and vein.[18] There were no changes in pulmonary and systemic haemodynamics in 10 patients with chronic obstructive lung disease and five otherwise normal patients with duodenal ulcers given ranitidine[19] nor in seven adults with portal hypertension given cimetidine.[20] A rise in pulmonary artery pressure was observed in a child given cimetidine for acute gastrointestinal haemorrhage induced by tolazoline, the pressure having previously fallen after tolazoline.[2] No measurements of pulmonary or systemic vascular resistances were made, however, on that child.

We conclude from our data that there may be H_2 receptors within the pulmonary and systemic circulations of children. The most probable explanation of our results is that stimulation of these receptors caused vasodilation and that blockade (at least of the stimulated receptor) caused vasoconstriction in both circulations. In addition, ranitidine seemed to have a direct negative chronotropic effect on the heart. These observations have clinical as well as theoretical importance. Clearly, H_2 receptor antagonists should not be used as treatment or prophylaxis for gastrointestinal haemorrhage induced by tolazoline, confirming previous findings.[2] The possibility of adverse cardiovascular effects in other children receiving oral H_2 blockers, particularly those with pulmonary hypertension, should be borne in mind. The safety of these agents in infants and children requires further investigation.

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Treatment of refractory supraventricular arrhythmias with flecainide acetate

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SUMMARY We treated 13 children aged 0·2 years to 15·7 years (median 7·1 years) with flecainide acetate for refractory symptomatic supraventricular tachycardia. Six children had direct atrioventricular accessory pathways, of whom four had overt Wolff-Parkinson-White syndrome on the 12 lead electrocardiogram, while in the other two the accessory pathway was concealed. Three children had nodal atrioventricular re-entrant tachycardia, two had a re-entrant tachycardia, the exact mechanism of which was not known, one child had ectopic atrial tachycardia, and one had atrial flutter associated with an atrial septal defect. The remaining 12 children had structurally normal hearts. Flecainide (2 mg/kg intravenously) resulted in termination of the tachycardia in 11 of the 12 children treated during tachycardia. In 11 of the children successful prophylaxis was achieved with oral flecainide. Side effects occurred in two children during intravenous administration, but there were no side effects with oral treatment. This experience indicates that flecainide, which has not been used extensively in children, is an effective and safe antiarrhythmic agent, capable of terminating and controlling supraventricular tachycardia in children. Furthermore, flecainide may be successful where conventional agents fail.

The incidence of supraventricular tachycardia in children is greater than 1 in 25 000.[1] Treatment with drugs may be problematic. An unknown proportion of these arrhythmias are refractory to conventional treatment and patient and doctor are subjected to a protracted and often unsuccessful process of empirical drug trials while control is attempted. Moreover, some of the agents have unacceptable side effects for children—for example, provocation of asthma with propranolol. There is a need for new effective antiarrhythmic agents, despite the wide range already available.

Flecainide acetate is relatively new and has been used successfully in adults for treatment of ventricular arrhythmias,[2] atrial fibrillation, atrial tachycardia, atrioventricular nodal re-entrant tachycardia, and atrioventricular re-entrant tachycardia associated with Wolff-Parkinson-White syndrome.[3] This agent has also been used to control junctional tachycardias in children.[4]

We report our experience in the use of flecainide for treatment of refractory supraventricular in arrhythmias in children

Patients and methods

Thirteen children (four boys and nine girls) were treated with flecainide. Their ages ranged from 0·2 to 15·7 years (median 7·1 years) (Table 1). Diagnosis was made either on 12 lead electrocardiogram (three children) or at electrophysiological study (10). Three children were found to have atrioventricular nodal re-entrant tachycardia associated with dual atrioventricular nodal pathways at electrophysiological study. In one of these children the tachycardia was incessant, and the other two suffered paroxysmal attacks.

Six children had direct atrioventricular accessory pathways. In four there was overt Wolff-Parkinson-White syndrome on the 12 lead electrocardiogram. In two the pathway was concealed. This diagnosis was made during electrophysiological study in one child and on the 12 lead electrocardiogram recorded during tachycardia when the R-R interval lengthened with left bundle branch block in the other child. All six children experienced paroxysmal re-entrant tachycardias and in case 1 the tachycardia

Table 1 *Details of the 13 patients with refractory supraventricular arrhythmias*

Case No	*Age (years)**	*Sex†*	*Diagnosis*	*Time of presentation to diagnosis of precise mechanism of tachycardia (months)‡*
1	0·2	M	Wolff-Parkinson-White syndrome with a concealed accessory pathway	0·5
2	5·6	F	Wolff-Parkinson-White syndrome	67
3	4·6	M	Nodal atrioventricular re-entrant tachycardia	48
4	13·7	F	Ectopic atrial tachycardia	0·7
5	7·3	M	Wolff-Parkinson-White syndrome	12
6	11·8	F	Wolff-Parkinson-White syndrome	132
7	7·1	F	Wolff-Parkinson-White syndrome	84
8	3·2	F	Supraventricular tachycardia§	—
9	6·4	F	Wolff-Parkinson-White syndrome with a concealed accessory pathway	48
10	15·7	F	Nodal atrioventricular re-entrant tachycardia	36
11	11·0	F	Supraventricular tachycardia§	—
12	8·7	M	Nodal atrioventricular re-entrant tachycardia	0·08
13	1·4	F	Atrial flutter	0·04

*Median age=7·1 years
†M=Male, F=Female
‡Median time to diagnosis=36 months
§Precise mechanism unknown

was so frequent as to be virtually incessant. In five of the six cases tachycardia was typical, using the atrioventricular node during anterograde conduction and the accessory pathway during retrograde conduction Case 5 had a variety of complex tachycardias in association with an atrioventricular direct accessory pathway and has been described elsewhere[5]

One child had incessant atrial tachycardia and one incessant atrial flutter. The precise mechanism for the tachycardia was not established in two children. The diagnosis of an atrioventricular re-entrant tachycardia was made on the 12 lead electrocardiogram recorded during tachycardia Neither showed any evidence of pre-excitation during sinus rhythm. One child had an atrial septal defect (case 13). The other 12 children had structurally normal hearts.

All children were having two to three attacks of symptomatic tachycardia each month, and in most of the children the attacks were more frequent (Table 2). In the older children symptoms during tachycardia were most commonly palpitations and lethargy. Some children experienced chest pain. The youngest infant, aged 7 weeks, rapidly developed congestive heart failure and therefore symptoms of poor feeding and tachypnoea.

All the children had been treated with at least one other antiarrhythmic agent, and most of them had resistant arrhythmias unresponsive to treatment with multiple drugs (Table 3) or had developed unacceptable side effects to a number of conventional agents

Treatment with antiarrhythmic drugs had been withdrawn to allow roughly three elimination half

Table 2 *Details of treatment with flecainide acetate in 13 patients with refractory supraventricular arrhythmias*

Case No	*Mode of initiation of tachycardia*	*Frequency of attacks before flecainide (per month)*	*Outcome of intravenous treatment*	*Duration of follow up (months)*	*Outcome of oral treatment*
1	Spontaneous	Incessant	Termination	3	No attacks
2	Induced	2	Termination	48	No attacks
3	Spontaneous	Incessant	Termination	32	Poor control
4	Spontaneous	Incessant	Termination	4	1 Attack*
5	Induced	4	Termination	48	2 Attacks
6	Induced	4	Termination	25	Poor control
7	Induced	10	Termination	18	No attacks
8	Spontaneous	12	Termination	3	1 Attack*
9	Induced	4	Termination	18	No attacks
10	Induced	10	Termination	15	2 Attacks†
11	Spontaneous	3	Termination	3	No attacks
12	—	12	Not treated	2	No attacks
13	Spontaneous	Incessant	Flutter cycle slowed, but failed to terminate	12	No attacks

* Attack associated with a reduction in dose
† Attack associated with a severe chest infection

Table 3 *Diagnosis and previous treatment with drugs in 13 patients with refractory arrhythmias*

Case No	*Diagnosis*	*Previous treatment with drugs*
1	Wolff-Parkinson-White syndrome	Amiodarone, verapamil digoxin, disopyramide
2	Wolff-Parkinson-White syndrome	Amiodarone, verapamil, digoxin, disopyramide, propranolol, phenytoin, lignocaine
3	Nodal atrioventricular re-entrant tachycardia	Amiodarone, verapamil
4	Ectopic atrial tachycardia	Verapamil, digoxin, propranolol
5	Wolff-Parkinson-White syndrome	Verapamil disopyramide, propranolol practolol
6	Wolff-Parkinson-White syndrome	Verapamil, digoxin, propranolol
7	Wolff-Parkinson-White syndrome	Verapamil digoxin, propranolol
8	Supraventricular tachycardia	Digoxin propranolol
9	Wolff-Parkinson-White syndrome	Verapamil propranolol
10	Nodal atrioventricular re-entrant tachycardia	Digoxin propranolol
11	Supraventricular tachycardia	Verapamil
12	Nodal atrioventricular re-entrant tachycardia	Propranolol
13	Atrial flutter	Amiodarone, digoxin disopyramide quinidine

lives to elapse before the flecainide was administered. Three children had received amiodarone. Two of these children stopped amiodarone one month before treatment with flecainide. In the case of the youngest patient (case 1) a period of only seven days had elapsed since the withdrawal of amiodarone. Amiodarone could not be detected in the infant's plasma, however, on the day of treatment with flecainide. Furthermore, digoxin concentrations in this patient were still within the therapeutic range, digoxin having been withdrawn only one elimination half life before treatment with flecainide.

Electrophysiological study was undertaken where necessary for full delineation of refractory supraventricular arrhythmias. Intracardiac studies were performed using standard techniques as described previously.[6] In all cases the reasons for carrying out

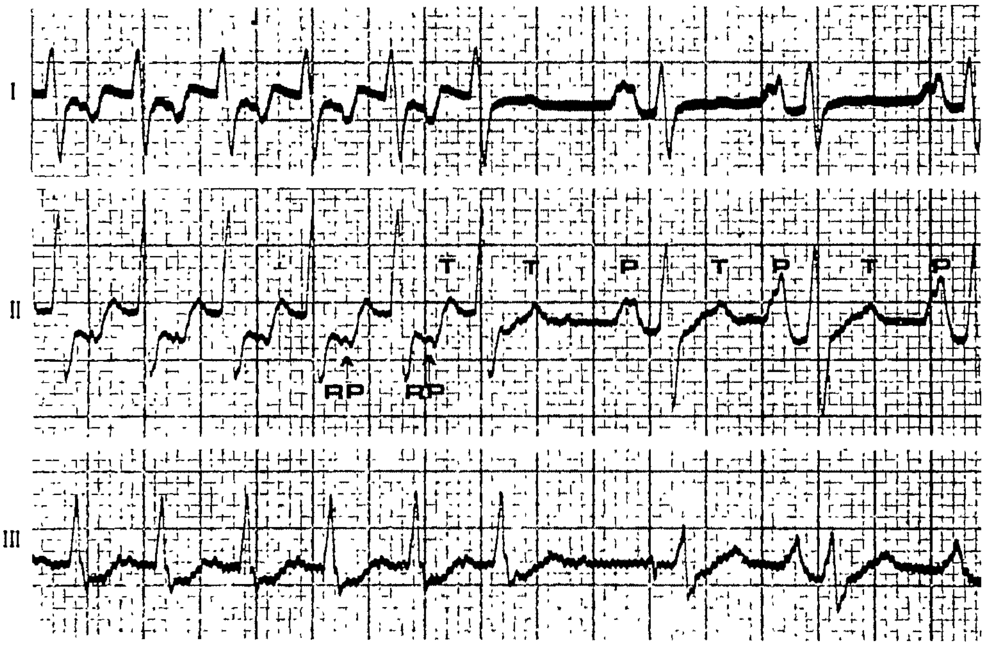

Fig 1 *Electrocardiogram of a case of atrioventricular re-entrant tachycardia, recorded in leads I, II, and III, showing termination in the limb involving the accessory pathway (retrograde limb) after intravenous flecainide acetate 2 mg/kg P=P wave, RP=retrograde P wave, T=T wave*

the study and for using flecainide were explained to the family and child and informed proxy consent obtained.

Flecainide was infused intravenously during tachycardia in 12 of the children In six the tachycardia was induced and flecainide given during electrophysiological study. In the other six the tachycardia occurred spontaneously and flecainide was infused while recording a 12 lead electrocardiogram A dose of 2 mg/kg was used over a period of not less than five to 10 minutes. The children were later begun on oral flecainide.

Results

In 11 of the 12 cases where tachycardia was present on administration of flecainide termination occurred within 12 minutes of the start of the infusion (Table 2). In case 13, who had atrial flutter, intravenous flecainide resulted in a slower flutter cycle but failed to terminate the tachycardia. In all 10 cases with re-entrant tachycardia flecainide terminated the tachycardia in the limb involving the accessory pathway In nine this was the retrograde limb of the circuit (Fig 1). The antidromic tachycardia in case 5 terminated as a result of atrioventricular block in the anterograde limb.

One child (case 3) developed proarrhythmic side effects during intravenous treatment. Only half the dose of flecainide had been given when the tachycardia slowed and terminated in the retrograde limb. Over the next two minutes sinus rhythm remained, but with increasing widening of the QRS complex (right bundle branch block morphology). This then gave way to repetitive multimorphic ventricular tachycardia. Isoprenaline was infused to counter prolonged intramyocardial conduction delay caused by flecainide Lignocaine and calcium were also administered intravenously. Ventricular tachycardia disappeared 10 minutes after the onset of infusion of flecainide and the QRS complexes gradually returned to normal over several minutes (Fig 2).

Only one child developed non-cardiac side effects. This child complained of transient nausea during the infusion of flecainide. The nausea disappeared within 10 minutes of stopping the infusion. No side effects were reported on oral treatment.

Of the 13 children, all but two suffered fewer

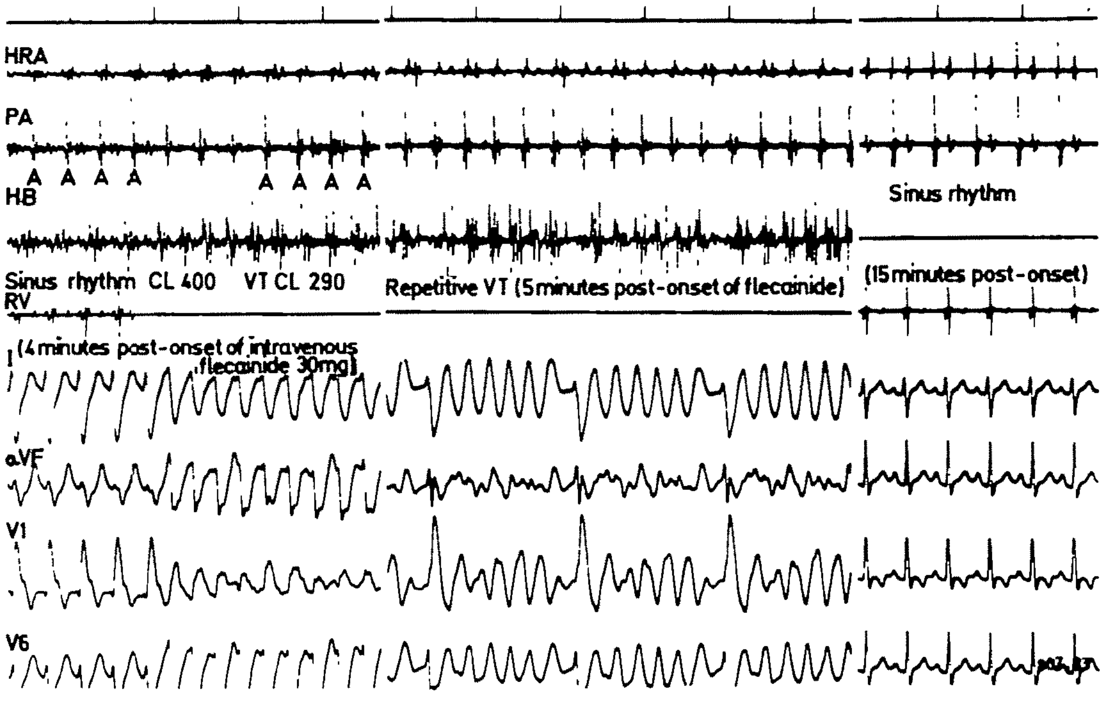
HRA
PA
A A A A
A A A A
HB
Sinus rhythm
Sinus rhythm CL 400
VT CL 290
Repetitive VT (5 minutes post-onset of flecainide)
(15 minutes post-onset)
RV
(4 minutes post-onset of intravenous flecainide 30mg)
I
aVF
V1
V6

Fig 2 *Repetitive multimorphic ventricular tachycardia (VT) recorded during electrophysiological study after administration of flecainide acetate (1 mg/kg) with restoration of sinus rhythm. HRA=High right atrial recording, PA=pulmonary artery recording, HB=His bundle recording, I, aVF, V1, and V6=surface leads, RV=right ventricular apex recording, A=atrial electrogram, CL=cycle length*

attacks each month than before treatment (median follow up 15 months) (Table 2). In two children flecainide terminated tachycardia acutely but failed to prevent recurrences Seven children have had no further attacks of tachycardia, including the child with incessant atrial flutter. In this child the atrial flutter failed to terminate during the intravenous infusion but after direct current conversion to sinus rhythm was maintained free of tachycardia with oral treatment.

Discussion

Flecainide acetate is a relatively new chemical agent with unique properties developed in 1966. It has been classified as a class 1c drug in the modified Vaughan Williams' classification.[7] Flecainide slows conduction throughout the heart, having its greatest effect on His bundle conduction. Refractoriness of normal atrial or atrioventricular nodal myocardium is not prolonged, but there is pronounced prolongation of refractoriness in anomalous tissue, such as accessory atrioventricular pathways [8]

Re-entrant junctional tachycardias are the commonest types of supraventricular tachyarrhythmias in children.[9] Nearly all such circus movement tachycardias involve the atrioventricular node. It is possible to terminate the circuit by delaying conduction through the atrioventricular node. This is the mechanism utilised by more conventional agents—for example, verapamil. In some situations, however, this may not terminate the tachycardia and may even affect the critical balance of the circuit and thus provide a situation that favours continuation of the tachycardia. In all our patients conventional atrioventricular nodal blocking agents had been used with little or no success. Flecainide may be successful in such situations because of the profound efficacy of the drug in delaying conduction and refractoriness in the accessory pathway The drug therefore provides an alternative approach to termination of circus movement junctional tachycardias.

In the child with atrial tachycardia flecainide terminated the incessant tachycardia where verapamil, digoxin, and propranolol had failed to do so. Tachyarrhythmias confined to the atria would not be expected to respond well to drugs that exert their major effect on the atrioventricular node. Such drugs had been used in this case because the precise mechanism of the tachycardia was not apparent until an electrophysiological study was undertaken.

The child with atrial flutter was also treated with a number of agents unsuccessfully before long term control was achieved with flecainide. In this case the mechanism of tachycardia was known, and treatment with drugs was appropriate but simply failed to control the arrhythmia. Flecainide failed to convert atrial flutter to sinus rhythm in this child. Preliminary reports suggest that flecainide is not particularly effective in the conversion of atrial flutter to sinus rhythm,[3] and the role of the drug in this situation has yet to be fully evaluated This child has remained in sinus rhythm for 12 months, however, taking oral flecainide, and the drug may be useful in preventing recurrence.

Flecainide has a prompt onset of action when used intravenously and terminated 11 of the 12 tachycardias within 12 minutes of the start of infusion. The drug was well tolerated both intravenously and orally. One child developed proarrhythmic side effects during intravenous infusion for reasons that are not clear Such side effects with flecainide have been reported in 7·5% of treated adults,[10] being more common in patients with pronounced left ventricular dysfunction. In stable patients, with normal ventricular function, the risk of initiating arrhythmias is likely to be less[11] and compares favourably with other class 1 agents [12] Electrocardiographic monitoring during intravenous administration with prompt termination of the infusion in the event of adverse electrographic signs such as widening of the QRS complex may help to minimise proarrhythmic effects.

Our effects suggest that flecainide will not only terminate but will also prevent recurrence of supraventricular arrhythmias in some children. Successful long term prophylaxis was achieved in 11 of the 13 children (median follow up 15 months) (Table 2)

In many of the children diagnosis of the mechanism of tachycardia was established only after considerable delay (Table 3), and in three cases this resulted in inappropriate treatment with drugs Electrophysiological study may be helpful in the management of supraventricular tachycardia in children It has become an established approach in adult practice and has transformed management, allowing not only precise diagnosis of the mechanism of tachycardia but also permitting the assessment of antiarrhythmic drugs. Suitable treatment with drugs may then be chosen based on the supposition that a drug that terminates a tachycardia and prevents reinitiation by intracardiac stimulation is likely to prevent spontaneous recurrence. Our data would support this supposition.

Our experience indicates that flecainide acetate is a safe, quick acting, and effective drug, both in the acute treatment and long term control of supraventricular tachycardia in children. Furthermore, flecainide may be effective where other more conventional agents have failed. Further information is required, but this report suggests that flecainide will be a useful drug in the management of supraventricular arrhythmias in children.

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Controlled trial of trimeprazine tartrate for night waking

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SUMMARY Mild hypnotics are often recommended for young children with sleep problems. This study assesses the efficacy of trimeprazine tartrate in 1 to 3 year old children with persistent and severe night waking in a double blind crossover trial with placebo. Children on treatment with trimeprazine had significantly fewer wakings, less time awake at night, and more night time sleep compared with those on treatment with placebo. There were no differences in these sleep variables when the first and last (fourth) week of treatment with drugs were compared. Follow up observations showed no significant difference in any sleep variables from baseline measures. The results are consistent with the idea that trimeprazine tartrate may be a useful short term treatment for night waking in young children.

Night waking is one of the most common behavioural problems in young children. Estimates for 1 to 3 year olds have varied from 10% to 23%, depending on the particular study and the age of the children.[1-3] Little is known of the aetiology of these sleep problems. Although numerous factors, including perinatal complications,[4 5] maternal responsiveness to crying,[4] birth order,[6] breast feeding,[7] and infant temperament[8] have been associated with night waking, the nature of the relation is uncertain. There is equally little certainty about treatment. In the past leaving the child to cry has been advised,[9] while more recent recommendations have emphasised the importance of consistent handling.[10-12] Some have thought that night time sedation is a useful treatment, especially in those children in whom other regimens seem to fail.[13] One recent survey suggested that as many as 25% of first born children received night time sedation at some point during the first 18 months.[14]

There have been a few studies on the efficacy of night time sedation in toddlers. One community survey reported that only 11% of parents whose children received hypnotics thought the medication had helped, but methodological problems in this study included the use of different drugs, unspecified dosages, and uncertain compliance.[15] A controlled study of diphenhydramine in children aged 2 to 12 years with various sleep problems showed treatment with the drug to be more effective than treatment with placebo, but the study did not examine differences due to children's age or the type of sleep problem[16] One trial that examined the efficacy of hypotics in young children compared trimeprazine tartrate with placebo in a double blind crossover design using parental sleep diaries and overall global ratings to assess response.[17] Trimeprazine tartrate was given for two weeks in a dose of 30–60 mg The results indicated some overall improvement in the children's sleep during treatment with the drug compared with treatment with placebo on composite scores of several sleep variables. The author, however, considered that the degree of improvement in sleep was only modest, and it did not persist at follow up six months later.

This moderate improvement in sleep suggested to us that such medication in higher doses, as recommended by some local general practitioners and paediatricians, and for longer periods might prove more beneficial in improving children's sleep while receiving medication and in 'breaking the habit' of night waking after the course of treatment was completed. The following study was designed to test these ideas.

Patients and methods

Children aged between 1 and 3 years with night waking were obtained by referral from general practitioners in Oxfordshire. Referrals were initially assessed and entered in the study if they met the entrance criteria and agreed to participate. The criteria were that the child should wake at least five nights a week and for at least 20 minutes a night. At the initial assessment evaluation included a detailed description of the child's sleep problem, an assessment of possibly relevant enviromental factors, history of antenatal and perinatal problems, a developmental history, and the family background of childhood sleep problems. The Denver developmental screening test was performed on all children

The study was a randomised, double blind crossover evaluation of trimeprazine tartrate given in a dose of 6 mg/kg (45–90 mg). A two week baseline period after the initial acceptance was followed by four weeks on either drug or placebo then a one week washout period followed by the other medication. All children were followed up one month after completion of the trial, when a semi-structured, standardised interview was carried out with the mothers to elicit childhood behaviour problems and parental psychiatric history.

Sleep was assessed by means of parental sleep diaries, which were kept throughout the trial These recorded the time of going to bed, going to sleep, and morning waking and time and duration of night time wakings and of daytime naps. Parents also completed weekly symptom checklists while their child was on treatment with drug or placebo and an overall treatment questionnaire at the end of each course. The study had received approval from the local ethics committee for research with human subjects.

Statistics. All analyses employed paired, two tailed t tests using the method described by Armitage for ascertaining period effects and treatment × period interactions in crossover trials.[18]

Results

Characteristics of the children. A total of 59 referrals were received, of whom 20 entered and 18 completed the study. Two children dropped out during the first treatment course, one because the mother thought the medication was giving her child nightmares and the other because the mother was unable to get her child to take the medication. Two mothers of children who completed the study lost or did not complete the diaries during the placebo period and their data were excluded from the diary analyses. The reasons why the other 39 children were not included in the study are given in Table 1.

For the 18 children who completed the study the mean age at the time of referral was 21·9 months, with a range of 7 to 37 months. Eight were boys and 10 girls. Four were only children, two were first born, and 12 were later born, indicating that first born children did not seem to be over represented in our sample. All social classes were represented

By maternal history, the wakeful children divided into two groups of nine children each. The first group had never settled at night and showed sleeping difficulties from birth and the second group seemed to sleep normally at birth, settling during the first few months, and developing night waking at a later date, often in conjunction with a minor physical illness such as otitis media. Many had received previous treatment with hypnotics with varying success.

Assessment of antenatal and perinatal adversity was based on maternal report alone; several mothers had required admissions to hospital for hypertension during the third trimester, two with subsequent induction of labour. One delivery was by caesarean section after prolonged labour. According to the history given by the mother, no child was

Table 1 *Numbers of and reasons for referrals not included in the study*

Did not want medication	11
Did not keep first appointment	9
Reported sleeping better	9
Did not keep second appointment	4
Inappropriate referral	4
Did not want to participate in study	2
Total	39

Table 2 *No of children with behaviour problems, with severity of those problems*

Area	*Degree of problem*	*No*
Eating		
	None	11
	Mild	3
	Moderate	3
	Severe	0
Temper tantrums		
	None	3
	Mild	4
	Moderate	10
	Severe	0
Disobedience/defiance		
	None	1
	Mild	5
	Moderate	8
	Severe	3
Miserable behaviour		
	None	4
	Mild	7
	Moderate	5
	Severe	1
Fears		
	None	6
	Mild	7
	Moderate	3
	Severe	1

appreciably delayed in developmental milestones Results of the Denver developmental screening test revealed only one child who scored below the 25th centile in any area.

Children's behaviour was rated for disturbance in five areas. Table 2 shows that the areas of disobedience/defiance and temper tantrums showed the greater number of moderate or severe problems. Although there was considerable variability in the number and severity of behaviour problems displayed by individual children, no child was without behaviour problems in spheres other than sleep but only one child showed two 'severe' problems.

Characteristics of the parents. By means of a standardised interview of the mothers, both parents were rated for past and present psychiatric history, with the threshold for disorder being consultation with the general practitioner or a psychiatrist. Eight mothers and five fathers had a past psychiatric problem. In the mothers the history was of depression in all cases, while in the fathers the history was divided between depression (three cases) and physical symptoms diagnosed as 'psychosomatic' (two).

Currently, six of the mothers rated themselves as depressed, although only one had consulted her general practitioner. Three of the fathers were currently suffering with psychosomatic symptoms and one had recently made a suicide attempt

Sleep diaries. Comparison of the mothers' descriptions of their children's sleep at initial interviews with baseline sleep diaries revealed a significant overestimation of the number of night wakings, with a non-significant trend to overestimate the time awake at night and to underestimate the total time asleep at the interview (Table 3). Many mothers seemed to be aware of the discrepancy, commenting after the baseline period that their children seemed to have slept better in the past two weeks.

Baseline measures for the group receiving drug first were compared with those of the group receiving placebo first to ensure their initial similarity. There were no significant differences between the two groups except on daytime sleep. This difference could not be explained by the age of the children and became non-significant when data on the two children whose placebo diaries were missing were added.

Table 3 *Comparison of mothers' descriptions of their children's sleep at initial interviews and baseline data from sleep diaries*

	Description	*Baseline measure*	*Mean difference (SEM)*	*p Value*
Total night time sleep (min)	563	590		NS
No of awakenings/night	4 6	2 8	1 8 (0 5)	0 001
Time awake at night (min)	61 3	51 6		NS

NS=Not significant

Sleep variables during treatment with drug and placebo were compared using the method described by Armitage (Table 4). While on trimeprazine, children slept longer at night, had fewer night wakings, and spent less time awake at night. No significant differences in daytime sleep were found. There were no significant period effects or treatment period interactions for any of the sleep variables, indicating that the effects of trimeprazine and placebo were independent of the order in which they were given.

Comparisons of all sleep variables in the first and fourth week of treatment with drug were made to assess whether trimeprazine retained its efficacy throughout the course of treatment. No significant differences in any sleep variables were seen.

Comparisons of the follow up diaries with baseline measures (Table 5) showed an overall improvement in sleep, with significantly fewer night time wakings and less time awake at night at follow up. As there was no period effect for the crossover, and hence no carryover effect from drug to placebo in the group given the drug first, the overall improvement at follow up was unlikely to be a direct effect of the drug

Parent ratings. The weekly symptom checklists revealed that a number of parents reported their children to be eating and drinking more while on trimeprazine. Three children had a bout of diarrhoea while on placebo. In their overall treatment ratings parents thought trimeprazine was significantly better than placebo on all measures of sleep,

Table 4 *Comparison of sleep variables during treatment with drug and placebo*

	Treatment		*Mean (SEM) treatment effect*	*p Value*
	Drug	*Placebo*		
Total night time sleep (min)	649	580	69 (12)	0 001
No of awakenings/night	1 4	2 4	1 0 (0 3)	0 001
Time awake at night (min)	22	41	19 (3)	0 001
Total daytime sleep (min)				
Group receiving placebo first	90	77		NS
Group receiving drug first	44	44		NS

NS=Not significant

Table 5 *Follow up at one month comparison of baseline measures and data from follow up diaries*

	Baseline	*Follow up*	*Mean (SEM) treatment effect*	*p Value*
Total night time sleep (min)	593	607		NS
No of awakenings/night	2·8	1·6	1·2 (0·3)	0·001
Time awake at night (min)	48·8	22·3	26·5 (5·0)	0·001
Total daytime sleep (min)				
Group receiving placebo first	43·8	42·8		NS
Group receiving drug first	86·0	57·3	27·7 (9·0)	0·05
Total sleep*	655	654		NS

NS=Not significant
*Total sleep refers to daytime plus night time sleep

with improvement in appetite and, in some cases, mood. In all but one case parents correctly guessed which course contained the active medication by the end of the trial.

Discussion

There are several factors limiting interpretation in this study. The data on which the conclusions are based, parental sleep diaries, are not completely objective, although every effort was made to simplify the recording of information and to encourage parents to keep accurate records. Furthermore, extremely poor sleep from the children was especially likely to lead to inaccuracies, with parents recording sleep as 'on and off' for several hours. It is noteworthy that most parents correctly guessed which course of treatment contained the active medication, and this may have biased their recording. Nevertheless, results of polygraphic sleep recordings performed on some of the children at home, by means of a small cassette recorder, have been compared with the parents' diaries and indicate, for the most part, that the parents' observations were accurate. (Simonoff EA, Stores G. Unpublished observations.)

The results of this study suggest that trimeprazine may be an effective treatment for reducing the number of night wakings and time awake during the night in young children. Furthermore, parents thought that trimeprazine was more helpful than placebo This is in contrast to the more anecdotal reports from one survey that suggested that medication did not improve the sleep of many children treated.[13] One possible explanation for this difference is the fairly high doses of trimeprazine used in this study. It is noteworthy that no adverse effects were observed at this dose and that the often cited side effects of daytime sleepiness and irritability almost always ceased after several days of treatment with the drug.

These results are roughly comparable with those reported by Richman[17] but, because the data are described in a somewhat different manner, direct comparisons are not possible. There is some indication that the children in our study had more night wakings on placebo, suggesting a more severe problem. Thus the fact that night wakings were reduced on average 40% (mean 2·4 wakings a night on placebo reduced to mean 1·4 wakings a night on medication) in our study compared with roughly 25% on average in Richman's report may reflect the greater initial severity of the problem in our sample, the effect of a higher drug dose, or some other factor or combination of factors.

The immediate effect of trimeprazine in reducing night wakings and the continued efficacy over four weeks are of clinical importance in considering this form of treatment for the sleepless child. The facts, however, that children continued to have some night wakings on these higher doses and that no carryover effects were shown mean that this treatment cannot be seen as a 'cure' but only as a helpful temporary measure in reducing night time wakefulness. It remains to be determined whether this type of medication would have any long term benefits were night time wakings eradicated completely during the course of treatment.

The children who participated in this study and their families are unlikely to be a representative sample of those presenting to general practitioners or health visitors with complaints of night waking. The children in this study probably represent more severe and long standing sleep problems and a greater degree of family psychopathology. Although we do not have control ratings on child behaviour problems and parental psychopathology, subsequent clinical experience suggests that the ratings in this study are likely to be underestimates of deviance, especially in terms of the children's behaviour. It is not possible from this study to predict the response to the medication of children with less severe and less complicated sleep problems. Night waking may represent the final common pathway for a number of disorders and difficulties with different aetiological factors, including biological vulnerability, psychosocial stresses, and family factors, as suggested by other investigators.[19] It may be that sleep problems with different aetiologies will show varying responses to treatment with hypnotic medication. The number of children in the study was too small to allow statistical analysis of subgroups, such as those with perinatal adversity.

The results described above indicate that trimeprazine in doses of 6 mg/kg may be effective in reducing night waking in young children without side effects. The problem may recur, however, when the medication is stopped. The results at follow up indicate that many children's sleep will improve over time, even if the problem is long standing before intervention. At present, it would seem reasonable to advocate the use of trimeprazine in this dose as a short term aid in reducing night waking. This can be used to give exhausted parents a break and allow both children and parents a period of sound sleep, either while waiting for the child to grow out of the problem or as a precursor to further treatment, such as a behavioural programme.

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Asthma and family interaction

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SUMMARY Patterns of family interaction were compared in the families of 22 children with chronic asthma, 30 children with diabetes mellitus, and six healthy children. The groups were similar in terms of age (range 4–14 years and mean 10·2 years). Peak expiratory flow and signs of allergy were correlated with family interaction in the subjects with asthma. The following significant findings were made. Family interaction was more disturbed in asthma compared with both the diabetic and the healthy groups. In most of the disturbed families interaction patterns were rigid and enmeshed, but a few showed chaotic and disengaged patterns. There was a negative correlation between peak expiratory flow and disturbed cohesion in non-steroid dependent cases. The severely ill children with asthma living in families with a normal cohesion score had higher IgE concentrations than children living in disturbed families. It is concluded that family interaction should be considered to be an important dimension in the investigation of severe childhood asthma.

Bronchial asthma is multifactorial and the relative importance of emotional factors in its pathogenesis has long been discussed. According to the current understanding the labile bronchial tract is viewed as the physiological substrate on which different precipitating factors exert their influence. The relative importance of allergy, infection, exercise, environment, and emotional factors must therefore be examined in each child [1]

Traditional psychosomatic research on asthma is strongly dominated by psychoanalytic theory. Empirical investigations of these theories, however, are contradictory. In children with severe asthma psychological disturbances have been shown to be more common than in the normal population but not more common than among children who suffer from other chronic physical disorders.[2]

Parental attitudes that reflect exaggerated concern in protecting the child's health[3] and overdependency on medical support[4] are common in cases of severe asthma. Although understandable in chronic illness, these represent maladjustments that block development of autonomy in the child and facilitate the expression of dependent needs and affects in somatic complaints.

If the causes of these relationship patterns are considered the onset of severe illness can be regarded as a traumatic crisis in which some children get stuck in the process of adjusting properly to a new way of living.[5] A lack of social contacts and relationships has also been found to be contributory[6] and the active efforts of paediatricians to prevent illness—that is, dietary regimens during pregnancy, prenatal screening—can cause the parents to focus too much attention on health problems.[7]

During the last few decades increasing interest in family treatment and research concerning family dynamics has yielded theories about specific interactional patterns and structure in families with psychosomatic children· enmeshment, rigidity, overprotection, poor conflict resolution, and involvement of the sick child in parental conflicts.[8] As far as childhood asthma is concerned these relationship patterns are thought to be present in the most severe 5–10% of cases[4] and positive results from treatment have been found [9] Some empirical support for this theory has been reported.[10] Communication in families with severely ill children with asthma (but not in mild and moderately ill cases) has also been shown to be disturbed.[11] The validity of the family diagnostic tools used in the first study, however, are characterised as unknown by the authors themselves,[10] and the findings of communication disturbances have no theoretical connection with the 'psychosomatic family' model [8]

An interesting theory of family function is that of Olson *et al.*[12] They have synthesised basic concepts that recur in the writings of different groups of family researchers/therapists into a 'Circumplex model of marital and family systems'. According to the model, all families can be placed along two dimensions, cohesion and adaptability. In the centre of the model are the 'balanced', functional families. Their degree of 'cohesion' is characterised by an equilibrium between intimacy and autonomy that permits family members to give and receive nurture and support but also to develop independently. Their degree of 'adaptability' is characterised by a balance between stability and ability to change. There is a combination of clear roles and rules of behaviour with a capacity to change during stress and according to developmental needs. Towards the periphery of the model are the 'extreme' and disturbed ('dysfunctional') family types. At one extreme their 'cohesion' is 'enmeshed', which is characterised by overinvolvement and overprotection, thereby giving little room for development of independence and autonomy. At the other extreme is the 'disengaged' family system where there is not enough involvement between the members. Each one feels lonely and neglected and the level of nurture and support is low.

The extreme positions on the dimension of 'adaptability' are 'rigidity' and 'chaos'. The rigid family has fixed rules for behaviour, roles, and modes of conflict resolution. These do not change when a new situation calls for innovation in coping. The system has thus a low capacity to deal with stress and ordinary change The chaotic family, on the other hand, has not developed enough routine for everyday situations. The duties and privileges belonging to each family member are diffuse and transient. Such lack of structure is energy consuming and interferes with coping.

The aims of the present study were to investigate family interaction in families of children with severe bronchial asthma and compare them with families of children with diabetes mellitus and families of healthy children. We used a family diagnostic instrument that has been tested for validity and reliability. The relation between clinical symptoms, as assessed by peak expiratory flow and signs and symptoms of allergy, and family interaction was also studied.

Patients and methods

Asthma groups. The children were selected by the paediatric allergist (N-IMK), based on clinical information of the somatic aspects of their asthma disease in their records, from roughly 600 cases with asthma who attend the paediatric outpatient department of the University Hospital, Linkoping, every year. Selection was based on the functional impact of the disease—that is, the number of days or nights a year with a decrease in activity or sleep due to asthma For participation the children had to be living in complete families.

Group 1
This group comprised the 14 most severe, chronic cases of asthma attending the clinic. They all had asthma grade D (early onset, severe non-remittent asthma) according to the criteria of McNichol and Williams.[3] Two families refused to participate in the study, so that 12 families were investigated.

Group 2
This group comprised 11 children attending the clinic with a previous history of asthma grade D, but who had improved and now had asthma grade C (continuous but episodic asthma[3]) for at least a year. One of these families refused to participate in the study, leaving 10 families who were investigated.

The 22 children in the two groups were similar regarding allergic symptoms (18 were considered allergic and 14 had atopic manifestations other than asthma). No child had any other serious disease. They all used bronchodilators and 21 also used sodium cromoglycate Eight of the 12 children in group 1 inhaled steroids compared with two of the 10 in group 2. Despite a large amount of medication, the cases who were taking steroids had somewhat higher disease activity and more symptoms and functional reduction due to asthma.

Groups 1 and 2 thus indicated only children who had, or had previously had, severe asthma. The children did not have any psychiatric disturbances according to the clinical judgment of the paediatrician (who had known the children for several years) and had not attended the child psychiatric department

Control groups.

Group 3
This group comprised 30 children with early onset diabetes. The children constituted all children in that age group who had been diagnosed as having diabetes for at least two years and were seen regularly at the paediatric outpatient department. These children were known (from another study) to have a similar distribution of different levels of behavioural disturbances as a normal group—that is, about 15% had psychological problems as revealed in an interview with the mother. They were considered to be a normal group of chronically sick children as far as psychological problems were concerned.[13]

Group 4

This group comprised six families who were asked to participate in this study to validate a test of family function. The children in this group were somatically healthy and had neither psychosomatic nor psychiatric disorders.

The groups were similar in terms of age (range 4–14 years and mean 10·2 years), sex, and number of siblings (in each group there was one family with a single child). Duration of disease was also similar in groups 1–3 (range 2–12 years and mean 7·2 years). Socioeconomic factors were comparable in the groups with asthma and diabetes, but in the normal group all families were upper middle class (Table 1).

Procedures. To obtain interactional material to rate, we followed the methods used by Minuchin *et al.*[8] They recommend standardised tasks that contain decision making, cooperation, and handling of conflict and differences. In this study the tasks consisted of planning a meal, furnishing a model flat, and discussing a recent conflict and aspects of family life that different family members liked and disliked. The families were given a brief outline of the procedure: they were told that the aim of the study was to investigate family function in chronic childhood disease but were not informed of our working hypothesis. Permission for videorecording was obtained in accordance with the human research ethics committee of the University of Linkoping.

The interaction tasks were presented to the family by a test instructor who then left the family to solve the issues on their own. The test instructor did not take part in the ratings. All families performed the family tasks once at entry to the study. All task performances were videotaped. The task performance situation and the videorecording obviously put stress on the family and was thus not an 'everyday' situation. It is in the reaction to a stressful situation, however, that the capacity to function adequately would really show. The stress in the test situation could thus be regarded as a simulation of other types of stress the family would meet at home [15] Only families with two parents (biological or remarried) were investigated.

A clinical rating scale, as modified by Cederblad *et al,*[16] was used. The instrument consisted of five variables on each subscale. In each variable there were operational definitions for low, midrange, and high scores.

On *adaptability* the variables were:

(1) Assertiveness (rigid (r),=always similar individual patterns; balanced (b)=individuals free to shift patterns; chaotic (c)=rapid, unpredictable changes).

(2) Discipline and control (r=dictatorial; b=mutually respected; c=laissez-faire).

(3) Consequences (r=strict and unavoidable; b=age appropriate; c=inconsequent).

(4) Rules (r=strict and unflexible; b=distinct; c=indistinct).

(5) Focus (r=gets stuck into details; b=focused attention; c=cannot keep focus).

On *Cohesion* the variables were:

(1) Emotional expression (disengaged (d)=low emotional responses; balanced (b)=adequate emotional responses, enmeshed (e)=overwhelming closeness).

(2) Attention (d=low; b=age appropriate; e=constant and intense).

(3) Support (d=lack of; b=given and taken; e=overprotection).

(4) Self reliance (d=too much independence; b=independence supported/accepted; e=independence actively discouraged).

(5) Decision making (d=individual; b=individual and family; e=no individual decisions allowed).

The clinical rating scale has been shown to differentiate well between families of healthy children and families of children who have child psychiatric symptoms[16] and also to be able to predict metabolic balance in adolescents with diabetes mellitus.[13]

The raters were experienced family therapists working in two pairs. They received at least 20 hours of training on the rating scales before rating the videotapes. The ratings were performed independently and without knowledge about which group each family belonged to. The time needed for rating each family was one to two hours. In the studies mentioned above[17 18] interrater reliability was measured to 0·69–0·74 on both adaptability and

Table 1 *Data on the families in the different groups*

	Group				
	1 (Grade D asthma)	*2 (Grade C asthma)*	*1+2*	*3 (Diabetes)*	*4 (Healthy)*
No	12	10	22	30	6
Sex (M F)	9 3	7 3	16 6	13 17	4 2
Age (years)					
Range	7–14	6–14	6–14	10–14	4–14
Mean	10 0	9 9	10 0	12 4	9 8
Duration of disease (years)					
Range	3–11	4–11	3–11	2–12	–
Mean	7 3	8 0	7 5	6 2	–
Social group*					
Upper	2	2	4	6	3
Middle	7	4	11	10	3
Lower	3	4	7	14	0

*According to Swedish National Statistics (1985) [14]

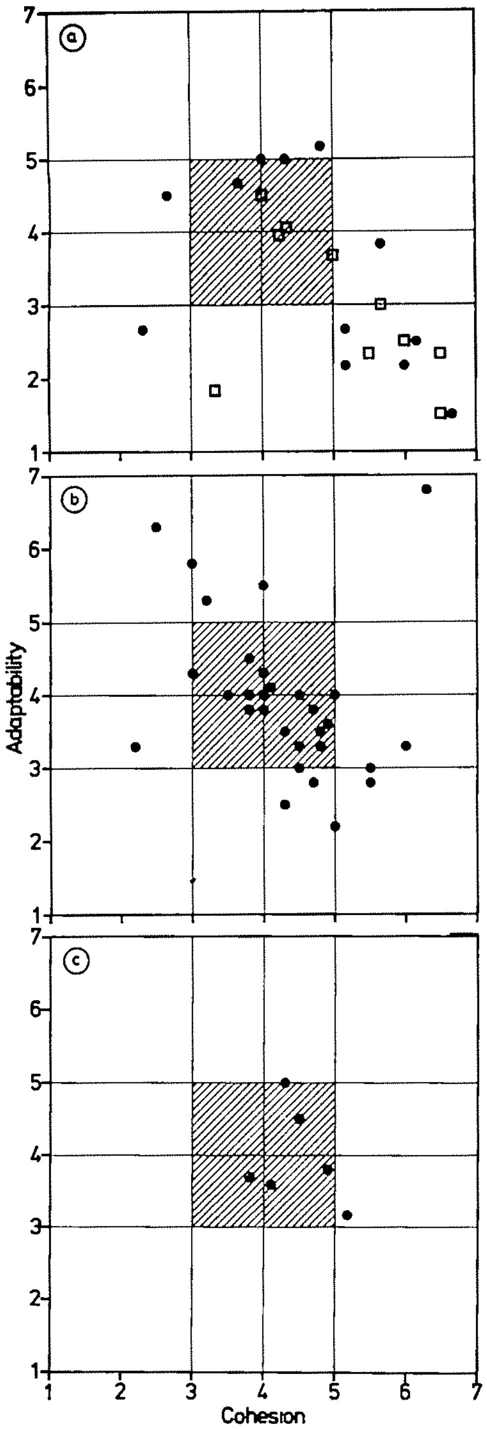

Fig 1 *Family interaction ratings (adaptability and cohesion) for the four groups (a) Groups 1 (grade D asthma) (●) and 2 (grade C asthma) (☐), (b) group 3 (diabetes); and (c) group 4 (healthy) Hatched areas represent balanced ratings.*

cohesion (Spearman's rank correlation coefficient).[17] Intraclass correlations (balanced versus disturbed) were measured to 0·56–1·0 on adaptability and 0·60–0·94 on cohesion. Pooled intraclass correlation was 0·69 on adaptability and 0·79 on cohesion (Cohen's κ).[18]

The asthma symptoms and reduction of function due to asthma were evaluated by a paediatric allergist for an observation period of three and half years and peak expiratory flow was measured with Wright's peak flowmeter. The best of three recordings was recorded and the predicted flow for body height calculated Serum IgE was determined with Phadebas IgE PRIST. The existence of allergy was determined without knowledge of the present grade of asthma severity Skin prick test (Pharmalgen) and radioallergosorbent tests (Phadebas RAST) were performed to food, animals, pollen, house dust mite, and moulds.

In the comparisons between the original groups, as well as in the comparison of signs and symptoms of allergy to family interaction, low and high rating scores were combined and called 'disturbed' scores, while the midrange (non-disturbed) scores were called 'balanced'. As both low and high scores were considered to be indications of disturbed family interaction the absolute value of the deviation from the median of the rating instrument was computed for the analysis of the relation between family interaction and peak expiratory flow. In this analysis the flow scores were correlated with the absolute value of the deviation from the median in the adaptability and cohesion scores

Statistical methods. For comparisons between groups the Fisher exact probability test (one tailed) was used. For measures of correlation the Spearman rank correlation coefficient was used. As our hypothesis indicated the predicted direction of differences one tailed tests were considered appropriate.[17]

Results

In the groups with asthma 12 of the 22 families were disturbed in the adaptability dimension and 13 in the cohesion dimension. In the group with diabetes nine of the 30 families were disturbed in the adaptability dimension and six in the cohesion dimension. The difference was significant ($p<0\cdot01$) in the cohesion dimension but not in the adaptability dimension (Fig. 1 (a), (b), Table 2).

Ten of the disturbed families of children with asthma showed rigid and 12 enmeshed patterns, and only two presented chaotic and disengaged interaction (Fig. 1 (a))

Table 2 *Group comparisons for adaptability and cohesion*

Group	*Adaptability*		*Cohesion*	
	Extreme	*Balanced*	*Extreme*	*Balanced*
1 (Grade D asthma)	7	5	8	4
2 (Grade C asthma)	5	5	5	5
1+2	12	10	13	9
3 (Diabetes)	9	21	6	24
4 (Healthy)	0	6	1	5

Adaptability groups 1+2 *v* 3, p<0·1, groups 3 *v* 4, not significant, groups 1 *v* 2, not significant
Cohesion groups 1+2 *v* 3, p<0·01, groups 3 *v* 4, not significant, groups 1 *v* 2, not significant

There was no significant difference in family interaction between the group with diabetes compared with the normal group of healthy children who were selected based on absence of psychiatric symptoms (Fig. 1 (b), (c), and Table 1).

A further analysis of the groups with asthma showed a few significant results, but in several comparisons the findings were not significant.

There was no significant difference in family interaction between group 1 (children with grade D asthma) and group 2 (children with grade C asthma) (Fig 1 (a), Table 2).

There was a negative correlation between peak expiratory flow and disturbed cohesion (Spearman's r=−0·58, p<0·05) (Fig. 2) in the non-steroid cases. No significant relation was found between the flow and family interaction in the steroid cases Mean flow scores were similar (85% of predicted) in the steroid and the non-steroid groups.

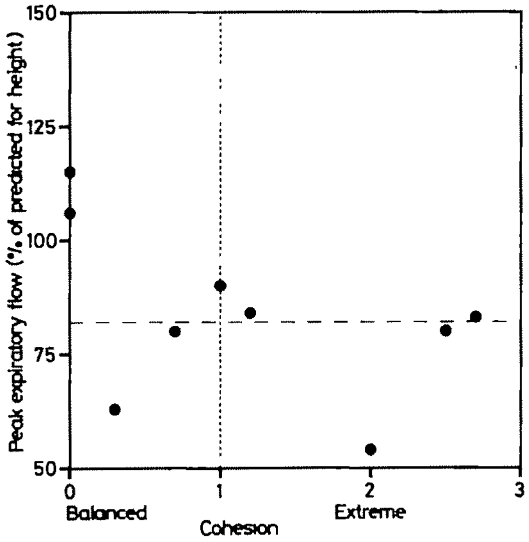

Fig. 2 *Family cohesion and peak expiratory flow in the children*

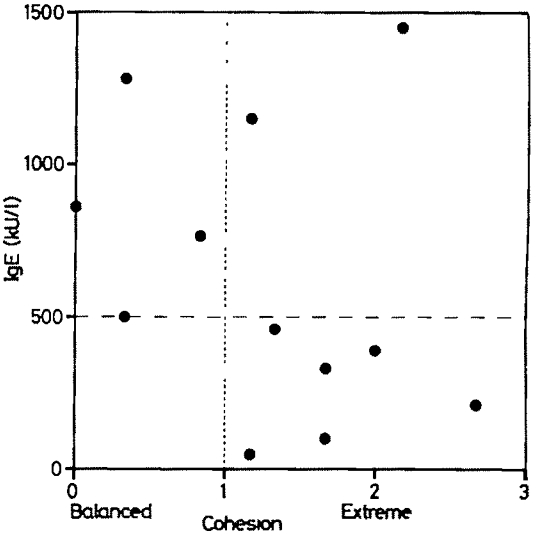

Fig 3 *Family cohesion and IgE concentrations in the children*

In group 1 the children living in families who were balanced in the cohesion dimension all had IgE concentrations above 500 kU/l. In contrast the children in six of the eight families with extreme cohesion had IgE concentration lower than 500 kU/l. This difference was significant (p<0·05) (Fig. 3) There was no difference between the groups with low and high IgE concentrations for age.

No such relation was found regarding the adaptability dimension and IgE. The signs of allergy showed no significant correlation with family interaction. In group 2 no clear relation was found between family interaction and IgE or between family interaction and signs of allergy.

Interrater reliability was 0·74 on both adaptability and cohesion measured with Spearman's r and 0·66 on adaptability and 0·94 on cohesion measured with Cohen's ϰ.

Discussion

We have shown that family interaction in the families of children with severe asthma was disturbed compared with other families with a severely, chronically sick child (diabetes). Interaction in the families of children with diabetes, on the other hand, did not differ from interaction in the families of healthy children. Families who had a child with diabetes were chosen as a control group because this disease puts tremendous demands on the family's capacity to adjust and function. If the disturbed family interaction in the families of children with asthma was a result of the chronic disease then the findings would have been similar in the families of children with diabetes. Furthermore, if the disturbed patterns were due to the disease, family interaction in group 2 (where the children's asthma had improved) should have been less disturbed compared with group 1 (where the children still had severe symptoms). Whether family interaction has any aetiological connection to bronchial asthma cannot be concluded from this study, but we are planning a prospective study to investigate this hypothesis further

The families of non-steroid dependent children with asthma were extremely enmeshed and rigid This was not so clear, however, in the steroid dependent cases. Some of these families were enmeshed, but others were disengaged and the adaptability scores were rather high—that is, more toward the chaotic extreme. The findings of Wirsching and Stierlin seem to be similar to ours—that is, a smaller proportion of the families were considered to be chaotic and disengaged.[19]

Airway resistance is easily influenced by suggestion and stress.[20] The negative influence on peak expiratory flow caused by disturbed family interaction cases indicates the importance of family relations in the management of the disease The fact that no such connection was found in the steroid dependent cases can probably be explained by the strong medication, which may have masked any psychological influence.

The finding that IgE concentrations in children with severe asthma were higher in the children living in balanced families was interesting. This could be interpreted as supporting the opinion that psychogenic factors are more important in cases of 'intrinsic' asthma [21]

As the children with asthma were selected only with regard to the clinical severity of their disease the families must be considered to be a representive sample of families of children with severe chronic asthma. The children were similar with regard to age, sex, and duration of disease.

Three of the 58 selected cases refused to participate in the study. These children (two in group 1 and one in group 2) did not differ from the others in their respective groups with regard to severity of disease

The rating instrument has not yet been completely developed and the stability of the test is somewhat uncertain. The results up to now, however, show good validity and interrater reliability and correspond well with clinical assessment.[16]

The results of this study support the hypothesis that disturbed family interaction is common in the families of children with severe, chronic, bronchial asthma and make it probable that the disturbed relationship patterns contribute to the severity of the disease in these cases.

The raters were Mrs Marianne Helgesson, Mrs Judit Ljungberg-Miklos, Magnus Ringborg, and Olof Ulwan Statistical advice was provided by Erik Leander, University of Linkoping Economic support received from the the Swedish Save the Children, the Swedish National Association against Heart and Chest Diseases, the Swedish Diabetic Association, and the County Council of Ostergotland is gratefully acknowledged.

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Nebulised sodium cromoglycate and verapamil in methacholine induced asthma

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SUMMARY Fifteen children with asthma underwent challenges with methacholine on separate days after double blind administration by nebuliser of either verapamil (5 mg), cromoglycate (20 mg), or saline (placebo). The provocation doses that produced a 20% fall in forced expiratory volume in one second (PD20) were analysed. There was variation in the protective effects of verapamil and cromoglycate among the patients. Although cromoglycate produced an increase in PD20 in 53% of the children tested, the protection was not significant when compared with the placebo. Verapamil was partially protective, however, in 80% of children and achieved significantly better results than the placebo. We suggest that this is likely to be due to a direct effect on bronchial smooth muscle.

One of the characteristic features of asthma is an increased sensitivity of airways to physical, chemical, and pharmacological stimuli, such as histamine, bradykinin, and acetylcholine or its synthetic analogue, methacholine.[1,2] Sensitivity to methacholine has become a valuable, reproducible, and widely used technique for studying irritability of the airways.[3]

There have been several studies since 1981 that have investigated the value of calcium antagonist drugs in blocking asthma induced by a variety of agents, and these have produced differing results. Studies to date have been predominantly on young adults with mild asthma. The purpose of this study was to compare the effects of the calcium antagonist verapamil with sodium cromoglycate, both administered by nebuliser, on bronchoconstriction induced by methacholine in children with moderately severe, extrinsic bronchial asthma.

Patients and methods

Fifteen children aged 7–13 years with asthma from a residential home for children with asthma (Villagio

Table 1 *Details of the 15 patients who entered the study*

Case No	*Sex*	*Age (yrs)*	*Height (cm)*	*Weight (kg)*	*Treatment*	*Duration of asthma (yrs)*	*Paper radioimmunosorbent test (U/ml)*	*Radioallergosorbent test*	
								Grass pollen	Dermatophagoides pteronyssinus
1	M	11	140	32	ISB,SCG,BDP	10	147	1^+	3^+
2	M	8	131	27	ISB	5	245	1^+	3^+
3	M	13	168	70	ISB,SCG T	5	1530	2^+	4^+
4	F	8	121	24	ISB,SCG	7·5	422	–	2^+
5	M	13	148	38	ISB	10	638	4^+	–
6	F	10	133	38·5	ISB SCG	5	491	–	1^+
7	M	10	133	25·8	ISB,SCG	8	833	4^+	2^+
8	M	13	168	70	ISB,SCG	6	1490	2^+	4^+
9	M	13	157	47·5	ISB	10	378	–	3^+
10	M	9	126	26·3	ISB,SCG,T	7	465	3^+	4^+
11	M	12	155	54·5	ISB	11	2940	3^+	4^+
12	M	7	131	30	ISB,T,BDP	6	1245	2^+	–
13	F	12	140	35	ISB,SCG	11	446	3^+	4^+
14	F	10	135	40	ISB	8	605	2^+	4^+
15	F	13	156	64	ISB,SCG,T	5	295	2^+	–

ISB=Intermittent sympathomimetic bronchodilators, SCG=sodium cromoglycate, T=theophylline, BDP=beclomethasone dipropionate

Alpino Pio XXII, Misurina, in the Italian Alps, with an altitude of 1756m) participated in the study. They all had reversible airways obstruction with skin tests positive to inhaled allergens and detectable serum IgE antibodies to at least one of three allergens (*Dermatophagoides pteronyssinus*, *D. farinae*, and grass pollen) (Table 1). None of the patients had had any upper respiratory tract infection in the four weeks before the study, which was carried out at high altitude and so minimised exposure to allergens[4 5] None of the children had hypotension, sick sinus syndrome, or atrioventricular block, which are contraindications to the use of calcium channel blockers.[6] Treatment with beta$_2$ sympathomimetics and cromoglycate was stopped 24 hours before the study, while slow release theophylline was stopped for one week. No patients were on oral steroid and only two patients (cases 1 and 12) were taking inhaled steroid, which was continued during the study. The children were considered to have moderately severe asthma, because they all required regular prophylactic treatment in their home environment and, despite treatment, still had frequent severe attacks that led to excessive absence from school. At the residential school treatment requirements and severity diminished considerably

Sodium cromoglycate (20 mg/2 ml), verapamil (5 mg/2 ml), or 2 ml saline solution as a placebo were administered by a Hudson nebuliser driven by compressed air at 8 l/min, 30 minutes before the challenge with methacholine, in a randomised double blind fashion. On the first day a baseline bronchoprovocation with methacholine was performed. During the next three days each patient was tested sequentially after each drug—that is, saline, verapamil, or cromoglycate. All tests were performed at the same time of day and were completed within four days. Forced expiratory volume in one second (FEV$_1$) was recorded by a Vitalograph wedge spirometer before and 30 minutes after inhalation of the drug but before provocation.

Bronchoprovocation with methacholine was performed with a 'Mefar' dosimeter, which can nebulise 0·01 ml of solution in 1·2 seconds. Thus 10 or 100 μg of methacholine solution (in phosphate buffer), using a 0·1 or 1% solution, respectively, is nebulised in 1·2 seconds The diameter of particles is 0·5–3·0 μ All the inhalations were performed by slow inspiration, starting from functional residual capacity without reaching total lung capacity followed by a five second holding of breath Before the provocation with methacholine five inhalations of buffer solution were performed. One minute after the last inhalation FEV$_1$ was recorded again and the challenge proceeded only if the change in FEV$_1$ was less than 10% Each patient received bronchoprovoca-

Table 2 *Values for forced expiratory volume in one second (FEV$_1$) before and after inhalation of placebo and active drugs (results are expressed as absolute values with percentage of predicted in parentheses)*

Case No	*Age (yrs)*	*Sex*	*Treatment*											
			Placebo				*Sodium cromoglycate*				*Verapamil*			
			Baseline FEV$_1$	*(% FEV$_1$)*	*FEV$_1$ at 30 mins*	*(% FEV$_1$)*	*Baseline FEV$_1$*	*(% FEV$_1$)*	*FEV$_1$ at 30 mins*	*(% FEV$_1$)*	*Baseline FEV$_1$*	*(% FEV$_1$)*	*FEV$_1$ at 30 mins*	*(% FEV$_1$)*
1	11	M	2 26	(105 6)	2 21	(103 2)	2 26	(105 6)	2 35	(109 8)	2 00	(93 4)	2 11	(98 6)
2	8	M	2 09	(117 4)	1 97	(110 6)	2 35	(132 0)	2 29	(128 6)	2 05	(115 2)	2 03	(114 0)
3	13	M	4 25	(119 0)	3 79	(106 1)	3 93	(110 0)	3 78	(105 9)	4 33	(121 2)	4 26	(119 8)
4	8	F	1 73	(120 9)	1 68	(117 4)	1 64	(114 6)	1 72	(120 2)	1 63	(114 0)	1 84	(128 6)
5	13	M	2 88	(115 2)	2 81	(112 4)	2 67	(106 8)	2 63	(105 2)	2 96	(118 4)	2 67	(106 8)
6	10	F	2 43	(130 6)	2 39	(128 5)	2 49	(134 0)	2 60	(140 0)	2 13	(114 5)	2 30	(123 7)
7	10	M	1 98	(102 2)	2 02	(104 2)	1 92	(99 1)	1 95	(100 6)	1 90	(98 0)	1 94	(100 0)
8	13	M	3 44	(96 3)	3 57	(99 9)	3 12	(87 4)	3 26	(91 3)	3 49	(97 8)	3 99	(111 9)
9	13	M	2 93	(99 0)	2 56	(86 6)	3 08	(104 2)	2 99	(101 0)	3 28	(110 9)	3 26	(110 3)
10	9	M	1·71	(107 0)	1 76	(110 2)	1 90	(118 6)	1 53	(95 8)	2 05	(128 0)	1 81	(113 3)
11	12	M	2 74	(96 0)	2 82	(99 0)	3 01	(105 5)	2 91	(102 0)	3 07	(107 6)	2 95	(103 4)
12	7	M	2 06	(115 9)	1 86	(104 4)	1 94	(109 0)	1 84	(103 2)	2 14	(120 4)	2 03	(114 1)
13	12	F	2 43	(113 7)	2 36	(110 3)	2 50	(117 0)	2 51	(117 4)	2 48	(116 0)	2 36	(110 3)
14	10	F	2 96	(132 6)	3 04	(136 4)	2 76	(123 6)	2 73	(122 3)	2 85	(127 7)	2 54	(113 7)
15	13	F	3 38	(116 8)	3 50	(120 8)	3 29	(113 6)	3 10	(107 0)	3 29	(113 6)	3 36	(115 7)
Mean			2 62	(112 8)	2 56	(109 7)	2 59	(114 8)	2 55	(110 3)	2 64	(112 9)	2 63	(114 2)
SD			0 71	(11 2)	0 68	(17)	0 62	(17 6)	0 62	(14)	0 75	(11 3)	0 78	(14 5)

tion with methacholine by increasing the number of inhalations of 0·1% methacholine solution to reach a total of 200 μg (20 inhalations). If a 20% fall in FEV_1 had not occurred the patient began inhalations of the 1% methacholine solution.

Data were plotted so that the cumulative units of inhaled methacholine appeared logarithmically on the abscissa and percentage decrease in FEV_1 compared with buffer control appeared arithmetically on the ordinate. The cumulative dose of methacholine to produce an exact 20% fall in FEV_1 (PD20) was calculated as described by Rosenthal[7] The results were analysed by Wilcoxon matched pairs test.

The parents of the patients gave informed consent and the protocol was approved by the hospital ethical committee.

Results

Baseline pulmonary function are presented in Table 2. Baseline FEV_1 was always above 80% of the predicted values for the height and age of the patients.[8] There was no difference in the baseline FEV_1 values during the whole study (p>0·1) and there was no bronchodilatation 30 minutes after inhaling verapamil, cromoglycate, or saline. The mean provocation dose of methacholine increased significantly with saline, verapamil, and cromoglycate compared with the preliminary baseline bronchoprovocation (Table 3) The PD20 on the day of administration of verapamil compared with the saline was increased in 12 and decreased in three of the 15 patients and on the day of administration of cromoglycate was increased in eight and decreased in seven. Although the mean PD20 increased on the day when verapamil was given and on the day when cromoglycate was given, this increase was significant compared with saline only for verapamil and not for cromoglycate (Figure and Table 3).

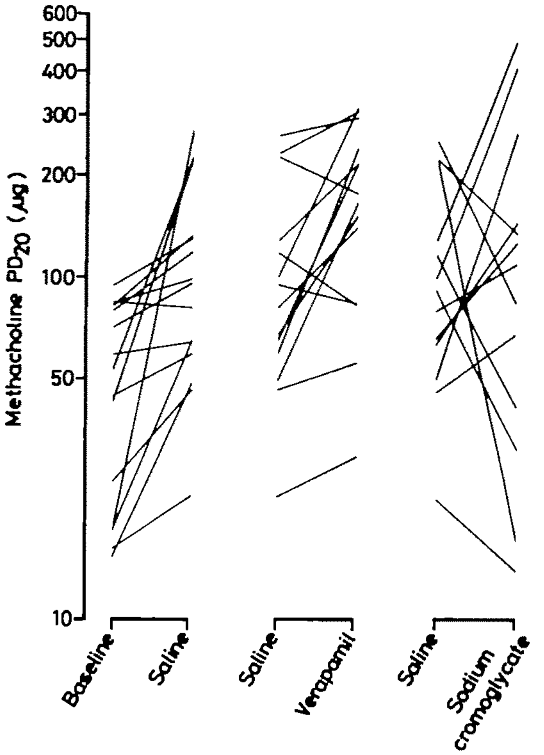

Figure *Influence of nebulised sodium cromoglycate and verapamil on methacholine bronchoconstriction (PD20) in 15 children with asthma*

Table 3 *Baseline PD20 FEV, and PD20 FEV, after inhalation of placebo (saline), verapamil, and sodium cromoglycate in the 15 patients*

Case No	*Baseline*	*Saline*	*Verapamil*	*Sodium cromoglycate*
1	60	65	210	150
2	80	120	82	43
3	18	67	155	130
4	72	97	85	32
5	55	230	180	135
6	25	47	57	70
7	45	60	245	58
8	16	23	30	14
9	85	82	143	112
10	85	102	325	430
11	95	130	220	510
12	83	135	150	145
13	42	235	315	17
14	15	50	170	275
15	18	265	300	85
Mean	52·9	113·9	178·4	147·1
SD	28·4	74·4	92·9	147·9

PD20=Provocation dose that produced a 20% fall in FEV_1, FEV_1= forced expiratory volume in one second Significance by Wilcoxon test of pair differences baseline *v* saline, p<0·01, baseline *v* verapamil, p<0·01, baseline *v* cromoglycate, p<0·01, saline *v* verapamil, p<0·01, saline *v* cromoglycate, p>0·05, verapamil *v* cromoglycate p<0·01

Discussion

Verapamil but not cromoglycate given by inhalation reduced sensitivity to methacholine significantly in our patients with extrinsic asthma. Other published studies have produced widely differing results on the degree of protection afforded by cromoglycate or calcium antagonists on bronchoconstriction provoked by cholinergic agents

Ryo and coworkers failed to show a significant change in responsiveness of airways to methacholine after inhalation of cromoglycate,[9] and other authors have shown similar results with bronchoprovocation with histamine.[10] Fabbri and coworkers found that a high dose of 40 mg of cromoglycate had a significant protective effect on the bronchial response to inhaled carbachol in six of eight patients tested,[11] while Patel recently reported that neither low nor high doses of cromoglycate protected the patients challenged with methacholine or histamine.[12] It has been suggested that the differing results of the studies of inhalation of cromoglycate on bronchospasm induced by histamine and methacholine may be explained by a variable bronchodilator effect of cromoglycate.[13] We were unable to show a bronchodilator effect of either cromoglycate or verapamil, perhaps because the patients had optimal lung function at the beginning of the study. Our findings on protection with cromoglycate are similar to those reported by Woenne and coworkers.[14] They found that some patients were protected by cromoglycate, although the effect was not significant when statistical methods were applied to the study group as a whole

Our observations are at variance with the findings reported by Patel, who showed no significant effect on bronchial reactivity induced by methacholine using verapamil in the same dose in adult patients with asthma.[15] Other studies have shown a wide range of effects of various calcium antagonists on bronchoconstriction induced by histamine, methacholine, exercise, hyperventilation, and antigen.[16] The discrepancies in results from various trials may be because the action of calcium antagonists may be dose dependent. In fact, the inhibitory activity of the calcium channel blockers have been shown to vary with the intensity of provocation and the dose of antagonist used For instance, at low concentration (10^{-7}m) acetylcholine was shown to cause voltage dependent calcium influx into canine tracheal smooth muscle, and this effect was inhibited by verapamil.[17] At high concentration (10^{-4}m) acetylcholine seemed to produce calcium entry independent of voltage, which was not blocked by verapamil.[16,17] Similar effects may occur in vivo. Doses of bronchoconstrictor agents used in the various clinical studies, however, cannot be compared easily because techniques of challenge and agents differed. Walters *et al* showed that the bronchoconstrictor effect of low concentrations of inhaled histamine was amenable to the inhibitory effect of verapamil but that once bronchoconstriction had occurred with higher doses of histamine the reactivity of airways was actually increased by verapamil.[18]

Other explanations for the variation in results may have been the utilisation of different methods of bronchoprovocation; varying age of the patients, severity of asthma, and its treatment before the study; and differing methods of statistical analysis. It is clear that bronchial hyper-reactivity is profoundly affected by the severity of asthma and can be decreased by effective treatment with either cromoglycate or inhaled steroids. Our patients had rather more severe asthma than is usual in patients chosen for challenge studies. We were able to conduct the study on these patients only because they were resident at high altitude, which resulted in improved control of their asthma.[5]

Free calcium ion availability in smooth muscles and mucous glands is thought to be a critical final pathogenetic pathway in asthma.[19] It follows, therefore, that reduction of calcium availability to essential contractile and secretory functions would be effective therapeutically. It is *unlikely* that they act by stabilising mast cells, as was hypothesised in earlier studies. A direct effect on the irritability of airway smooth muscles by limiting free calcium ion availability is an attractive alternative explanation.

There is now a large bibliography on the inhibitory effects of single doses of calcium antagonists on artificially induced airflow limitation in subjects with asthma. Extrapolation of the results of such studies to the clinical situation is often misleading, as is apparent from the apparent lack of effect, in our study, of the often clinically effective drug, cromoglycate. Similar, even more dramatic, discrepancies are observed with corticosteroids. We think that our study on children with moderately severe asthma indicates that clinical investigation of the therapeutic role of calcium antagonists is now required.

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Fifty years ago

Pellagra in African children

H C Trowell (Uganda)—Arch Dis Child 1937;**12**:193–212

The author described his observations on 24 African children aged from 1 to 4 years who were admitted to hospital in Nairobi Clinical features included misery, irritability, anorexia, and extreme listlessness Oedema was universal, usually severe and generalised, and if it disappeared great emaciation was revealed. Skin manifestations included jet black areas of hyperkeratosis, which showed a tendency to exfoliate, disclosing areas of pink or pale skin Sodden areas of heaped up white skin or excoriation were seen near mucocutaneous junctions (mouth, nose, canthi, and anus) Fissures, often deep and linear, developed at the flexures Generalised hypopigmentation was usual The hair came out easily, was thin and brittle, and changed colour Septic skin lesions were common. All cases were associated with diarrhoea, and steatorrhoea was pronounced in most. Neurological changes were rare apart from hypotonia and wretchedness, but eight patients exhibited hypertonia, increased tendon reflexes, and extensor plantar responses Another common finding was photophobia with red eyes In most children there was a microcytic hypochromic anaemia; in three a macrocytic anaemia was found

In his discussion Trowell noted that the clinical and laboratory features, particularly the pronounced oedema, distribution of the skin lesions, steatorrhoea, and rarity of neurological signs differed from the classical description of pellagra in adults and he was aware that other workers in tropical Africa had concluded that the disease under study was not pellagra. He maintained, however, that this syndrome in young children did reveal the main clinical signs of pellagra, and he observed that other known deficiency states—for example, scurvy, and rickets/osteomalacia—display a different clinical picture in children and adults Indeed he stated, "It is not suggested in this article that the disease is anything but pellagra"

Comment. Fifty years ago there was much confusion about the nature of the disorder as described by Trowell and others on the east coast and the disorder described by Cicely Williams and others in west Africa. Today Trowell's patients would be accepted as undoubted examples of kwashiorkor and the confusion has long since been resolved. It should be remembered, however, that it is possible for pellagra to coexist with kwashiorkor. Furthermore, the manifestations of kwashiorkor may differ in various geographical areas due to superimposition of additional deficiencies—for example, B complex, vitamin A, iron, and folic acid.

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Prolonged exclusive breast feeding and heredity as determinants in infantile atopy

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SUMMARY We followed 183 infants for two years, 31 of whom were breast fed less than three and a half months (median 70 days; short breast feeding group) and a further 31 of whom were exclusively breast fed for more than nine months (long breast feeding group). We assessed heredity for atopy, number of infections, and duration of breast feeding as determinants of atopy. During the first year of life 14 infants has signs of atopy. During the second year parents reported signs of atopy in a further 31. Heredity was the only significant predictor of atopy. Atopy was seen in 33% of infants with a positive heredity and in 16% without family history for atopy. The duration of breast feeding affected the incidence of atopy only among the infants without family history for atopy: fewer in the short breast feeding group (1/18) had atopy than in the long breast feeding group (5/13). Duration of breast feeding did not associate with incidence of respiratory infections. Diarrhoea was more common in the short breast feeding group than in the long breast feeding group during the first year of life. We conclude that prolonging exclusive breast feeding from the median of 70 days to nine months did not contribute to the prevention of infantile atopy and respiratory tract infections.

Human milk is the best nutrition for the full term human infant during the first months of life, but nutritional needs can also be met accurately by a well balanced formula. The non-human proteins in the formulas, however, always provoke immune reactions in the infants and, furthermore, the formulas lack the protective agents of human milk.[1] Many studies have indicated that infants on cow's milk or formulas based on cow's milk have more gastrointestinal and also probably more respiratory infections than breast fed infants[2–6] A higher number of infections as well as immune reactions to cow's milk proteins may pave the way for atopy, which may be more common in infants who are weaned early than in breast fed infants[4 7 8–13] This has been disputed, however,[7 14] particularly in more recent studies.[15–20]

During a prospective nutritional study on 198 infants[21] we carefully recorded all signs of atopy and infections and studied the interrelations with the feeding regimens.

Patients and methods

Follow up. Participants were recruited from mothers who had given birth to healthy babies at the department of obstetrics of the University of Helsinki. They were invited to participate on certain, predetermined days. Prerequisites for inclusion were that they were non-smokers, lived in the city of Helsinki, did not have any major disease (atopy was not a reason for exclusion), and had a full term, appropriate for gestational age baby. Altogether 90% of those asked agreed to participate. The goal was to obtain 200 newborn infants for the study. Two families dropped out during the first year, leaving 198 infants.

The infants visited the paediatric clinic at 2, 4, 6, 9, and 12 months of age. At each visit all relevant data were recorded and a physical examination made. We provided all medical care—for example, treatment for respiratory infections—during the first year. At a mean age of 2·3 years 60 of the infants were again studied The parents of all 198 infants were asked to complete a questionnaire about the health of their infant during the second year of life; 15 families failed to return the questionnaire.

Feeding. We encouraged mothers to carry on exclusive breast feeding as long as possible to study its nutritional value. Exclusively breast fed infants received no formula milk or other complementary food. Their number gradually fell to 101 by the age of 6 months and to 31 by the age of 9 months (long breast feeding group) The median duration of exclusive breast feeding in this group was 323 days, and most were fully weaned only after 12 months.

The infants who were completely weaned followed a standard dietary programme, which included an adapted formula with 16 g/l protein (Valio Co Ltd, Helsinki, Finland), fruit and vegetables from 3 months, and cereals and meat from 5 months; pasteurised whole cow's milk was substituted for the formula from 9 months Thirty one infants were completely weaned by 3·5 months; they were all breast fed from birth, exclusively for a median of 11 days and at least partially for 70 days (range three to 105 days; short breast feeding group). The cut off point of 3·5 months was chosen to obtain an appropriate number of infants for comparison

Heredity for atopy. Seventy nine infants had one or both parents or a sibling with atopic symptoms (bronchial asthma, allergic rhinitis, atopic dermatitis, or recurrent gastrointestinal symptoms occurring within one hour of ingesting particular foods).

Environment. Social class, education of parents, and housing conditions of the infants were recorded The type of day care they received during three month periods was classified as home care, day care in a small group, and day care in a large group outside the home. There was practically no smoking in the homes, and smoking was forbidden in the day nurseries.

The social class of the families (determined on the basis of the father's position) was similar in both the short and long breast feeding groups (42% and 44%, respectively, in the highest social class). The mean age of the mothers in the long breast feeding group was significantly higher compared with those in the short breast feeding group (30·9 *v* 27·7 years, p=0·001). Also the number of mothers with academic or other tertiary education was higher in this group (58% *v* 42%, p<0·05).

Atopy. Atopy was diagnosed if the infant had the following:

(1) Pruritic dry dermatitis, consisting of erythema or papules outside the nappy area, which was present on two or more visits during the first year.

(2) A history of urticarial eruption

(3) Three or more episodes of wheezy bronchitis during one year.

(4) Three or more of the following symptoms: rhinorrhoea for more than one month; itching or watering eyes; gastrointestinal symptoms provoked by foods; one or two wheezy attacks of bronchitis during one year.

(5) Dermatitis described by the parents to be compatible with atopic eczema during the second year.

Statistical analysis. We used χ^2 and t tests for comparisons.

The predicting factors for atopy were analysed by stepwise logistic regression. The following variables were tested as basic variates·

(1) Education of mothers.
(2) Size of home.
(3) Type of day care (period of more than six months during the second year).
(4) Heredity for atopy.
(5) Age at first exposure to cow's milk (formula)
(6) Age at start of regular formula feeding.
(7) Total duration of breast feeding.
(8) Age at introduction of solid foods.
(9) Number of respiratory tract infections during the first year.

The predictive variates were treated in the first analysis as continuous (variables 2, 5–8, and 9) or categorical (variables 1, 3, and 4). In further analysis all variates were treated as categorical.

Results

Atopic manifestation. Fourteen infants had signs of atopy during the first year (7% of total) and a further 31 (17%) had signs suggestive of atopy during the second year. Only three infants had symptoms suggestive of asthma.

Logistic regression analysis showed heredity for atopy to be the only significant factor for predicting the occurrence of atopy (χ^2=4·33, df=1, p<0·05), and the relative risk for atopy among those with a positive heredity was 1·41 (95% confidence limits=1·00–1·98). More infants with heredity for atopy had signs of atopy during the second year than those without heredity (p=0·04) (Table 1) Exclusive breast feeding lasting more than six months was a probable risk factor for atopy, with a relative risk of 1·37 (95% confidence limits=0·96–1·96) (χ^2=3·44, df=1, p<0·1). The effect of feeding on the incidence of atopy was seen among infants who did not have a family history of atopy, the incidence of infantile atopy being higher in the long breast feeding group (exclusively breast fed for more than nine months) than in the short breast feeding group (p=0·06) (Table 2). After the effect of heredity had been disregarded, atopic manifestations during the first year were more common among infants in the long breast feeding group (p=0·02) (Table 1). The proportion of infants with heredity for atopy in the two groups was similar (Table 2).

Table 1 *Atopy in groups with varying duration of exclusive or total breast feeding, in infants with heredity for atopy, and in groups with different incidence of respiratory infections*

Group	*No of children*	*Atopy occurring during first year of life (% of infants)†*	*Atopy occurring during second year of life (% of infants)‡*
Short breast feeding (<3·5 months)	31	0*	13
Long exclusive breast feeding (>9 months)	31	16*	15
Exclusive breast feeding >6 months§	101	7	23
Heredity for atopy	79	9	24**
No heredity for atopy	119	6	10**
Frequency of upper respiratory tract infections during first year			
High (>6)	53	9	10
Moderate (3–5)	103	6	15
Low (0–2)	42	7	22

*p=0·02, **p=0·04
†Information available for 198 infants
‡Information available for 183 infants
§Median duration of exclusive breast feeding was 278 days, most infants were fully weaned after 12 months

Table 2 *Incidence of atopy during the first two years according to duration of exclusive and total breast feeding and heredity for atopy in selected groups of infants*

Type of breast feeding	*No heredity for atopy*			*Heredity for atopy*		
	No atopy (No)	*Atopy (No)*	*Incidence (%)*	*No atopy (No)*	*Atopy (No)*	*Incidence (%)*
Short total (<3·5 months)	18	1	5*	9	3	25
<6 Months	26	4	13	12	3	20
>6 Months exclusive	47	12	20	30	13	30
Long exclusive (>9 months)	13	5	28*	9	4	31

*p=0·06

The occurrence of atopy did not differ significantly in infants with a low, moderate, or high incidence of upper respiratory tract infections (Table 1). Logistic analysis showed that this factor had no significant risk for atopy. The other seven variables tested (see methods), including age at introduction of solid foods, were not risk factors either for atopy.

Infections. Fewer of the infants with long exclusive breast feeding had acute diarrhoea during the first year compared with those with short breast feeding (5/31 *v* 12/31, p=0·06) The number of other infections in these feeding groups was similar. In the whole study group of 198 infants the mean number of upper respiratory tract infections during the first year was 4.3 and during the second year was 3·0. The respective figures for otitis media were 0·4 and 1·5 and for diarrhoea were 0·4 and 0·6. The infants received on average 0·5 treatments with antibiotics during the first year and 2·2 during the second. The number of infections was similar in infants with and without atopy. The group with atopy, however, may have been treated more often with antibiotics during infancy The mean number of treatments during the first two years was 4·2 for those with and 2·2 for those without atopy (p=0·05).

Discussion

Since the early 1970s breast feeding has regained its popularity. In Finland the proportion of infants breast fed for six months has grown from less than 10% in 1970 to 25% in 1977 and to 69% thereafter. Prolongation of maternity leave and change in attitudes towards artificial feeding have been largely responsible for this Today, the message of the presumed health benefits of breast feeding is spread through popular magazines and baby health clinics, putting great pressure on nursing mothers to carry on breast feeding for as long as possible. It is therefore not surprising that when we encouraged the mothers in our study to breast feed their infants exclusively half of them did so for six months and 31 for nine months.

Our study group was selected to include only healthy newborn infants of non-smoking mothers who had no major illness. Participation was high (90%) and the number of dropouts low (1%). No bias was likely to be caused by these factors. We believe, therefore, that our results give a realistic picture of the incidence of atopy and infectious diseases among healthy infants living in a developed urban society.

Several earlier studies have shown that breast feeding (exclusive or mixed) prevents or postpones the development of atopy.[4 7–13] According to most studies, however, the source of the artificial feeding (cow's milk or soy) does not influence the incidence of atopy.[13 14 22] Earlier studies have also shown that breast feeding does not prevent atopy [15–20] One recent study[20] and our present results even show the contrary—namely, fewer atopic signs in early weaned infants.

Some studies have shown that the early introduction of solid foods is a risk factor for atopy,[15 23] but we did not find any such association. We did, however, introduce solid foods late and gradually, which may have an influence.

We speculate that the lower protein concentration of presently used formulas compared with earlier ones makes them less antigenic. This may partly explain why the artificial feeding did not provoke atopy as often as in earlier studies.

In our study, as in many others, heredity for atopy was significantly associated with the occurrence of infantile atopy.[11–18 20 22] Earlier studies have suggested that breast feeding is particularly protective against atopy in infants with a positive heredity for atopy,[11–13 20 22] but we saw no evidence of this effect. On the contrary, in infants without such heredity a short duration of breast feeding was associated with a lower incidence of atopy, whereas a long duration of breast feeding was not. We also considered the possibility that the mothers tried to treat their infants' atopic like symptoms by prolonging breast feeding. The motivation to breast feed, however, was high in all mothers and breast feeding was stopped when the amount of milk became insufficient for the baby. Sensitisation through breast milk could be another explanation. Breast milk carries small quantities of food proteins in antigenic form,[1] which may provoke synthesis of IgE antibodies and clinical hypersensitivity. In fact, in a recent study this type of sensitisation was seen in 10% of breast fed infants.[24]

The protection by human milk against infectious gastrointestinal diseases is well known, particularly in developing countries and in infants with malnutrition.[2–4 7] We also found that fewer infants on prolonged breast feeding had acute diarrhoea during the first year than infants put on formula before 3·5 months of age.

Some studies suggest that human milk may protect against respiratory tract infections,[2 4] in particular otitis media,[6] but these findings have been disputed.[7] It is generally agreed that colostrum milk antibodies are not absorbed from human milk,[1] and hence the protective effect of breast milk is difficult to explain. We did not see any difference in the rate of respiratory infections between infants with short and long breast feeding.

In conclusion, our study showed that in a highly hygienic society prolonged exclusive breast feeding had no advantage over short breast feeding with regard to the risk of atopy or respiratory infections during the first two years of life. We emphasise that our results may not apply to undeveloped societies where the incidence of intestinal infections is much higher and malnutrition of mothers and infants common.

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Commentary

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The notion that atopic disease can be prevented by breast feeding is surrounded by confusion. There is a pitiful lack of good objective data. Not one study of this subject is without serious defect, and those from the greatest enthusiasts for this new religion are often the most riddled with flaws. Objections to previous studies, where the incidence of eczema or atopic disease was compared in babies fed in different ways, include:

(1) Observer bias: Doctors known to be protagonists of breast feeding decided whether to classify an infant's skin rash as 'eczema' or not, a procedure notorious for its lack of objectivity, in the full knowledge of both the family history and whether the baby was breast or bottle fed

(2) Misleading information based on inclusion of minor forms of disease. Studies compared the total incidence of diseases such as eczema or asthma in babies fed in different ways, but mothers fear *severe* cases. It would be a waste of time to find a technique that abolished hairy patches over the sacrum but failed to prevent spina bifida.

(3) Self selection bias. Inevitably, mothers with a strong family history are the ones most motivated to try a possible preventive measure and yet their offspring are at the greatest risk of being affected, making comparison with another group difficult or impossible.

In this context, there is only one fact that is really clear about breast feeding, which has been known for 50 years or more but has been recently rediscovered. This is that in certain women ingested food antigens can pass into the milk. Maternal avoidance of the food in question is followed by remission of atopic disease in the infant, and re-exposure is followed by relapse. It is probable, though unproven, that mothers susceptible to this problem are themselves atopic. Thus the very women who might most wish to prevent atopic disease in their offspring may be just the ones in whom breast feeding contributes to the production of atopic disease.

The latest paper from Helsinki is by no means free from defects, including some of the ones described above, but it is better than most. The authors' carefully worded conclusion is that prolonged breast feeding did not prevent atopy. For cases where there was no family history of atopy, however, the *greater* incidence of atopic disease in those infants receiving prolonged exclusive breast feeding almost reached significance. The message for obstetricians and paediatricians is clear The idea that eczema or asthma can be prevented by breast feeding, whether or not accompanied by other forms of antigen avoidance such as the delayed introduction of solids, seriously lacks objective validation

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Hypercholesterolaemia treated by soybean protein diet

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SUMMARY After a period of stabilisation on a controlled low lipid low cholesterol diet with animal proteins a group of 16 children with familial hypercholesterolaemia were given a textured soybean protein based diet, with a similar fat composition. All the children had a highly significant reduction in total cholesterol, averaging −21·8% against the baseline after eight weeks. Compliance became less strict afterwards, but more than half of the patients have regularly continued the diet and results have been maintained for one year. Minimal changes were noted in triglyceridaemia and in high density lipoprotein cholesterol concentrations, which showed a slight rise only at the end of treatment. The children's growth during the trial was normal. In view of the psychological difficulties of prescribing treatment with drugs to children with severe hypercholesterolaemia before puberty and of the relative ineffectiveness of standard low lipid diets in this condition the soybean protein diet may offer a satisfactory alternative.

Hypercholesterolaemia in childhood poses serious therapeutic problems, in that treatment with drugs, although reported as well tolerated,[1] often conflicts with the physician's desire to avoid chronic treatments during growth. Dietary studies, on the other hand, characterised by a moderate cholesterol intake with increased polyunsaturated/saturated (P/S) fatty acid ratios, often lead to fairly modest plasma cholesterol reduction.[2 3]

More recently, the observation that switching from a low lipid diet with animal proteins to a similar diet with textured vegetable proteins (TVP) extracted from soybean markedly reduces cholesterolaemia in adult patients with type II hypercholesterolaemia has attracted considerable attention. An attempt to modify the type of dietary proteins in children with hypercholesterolaemia has already been carried out, using a vegetarian type of diet (including 60% animal proteins, mostly from milk) with a high linoleic acid content (P/S ratio 1·6)[5] Compared with a 'control' diet, with a similar P/S ratio, this vegetarian diet lowered cholesterolaemia by roughly 10%.

As it seems possible, based on our extensive experience in adult patients, to provide a reasonably well accepted dietary regimen, by totally substituting animal proteins with TVP from soybean, now provided with added lecithin (L-TVP),[6] we decided to test this dietary approach in a selected group of type II children.

Patients and methods

Sixteen prepubertal subjects, with an age range of 3 to 12 years, were included in the study. All came from families known by the investigators of the three participating centres (Bologna, Milan, and Mendrisio) to have a high prevalence of hypercholesterolaemia. All the children presented with a low density lipoprotein (LDL) cholesterolaemia in excess of the 90th centile according to accepted guidelines[7] as well as for the Italian population of their age.[8] In addition, they either presented with tendon xanthomatosis or with a hypercholesterolaemic first degree relative with xanthomatosis and coronary disease. In one case (case 4) a diagnosis of homozygous type II disease was made, based on the clinical findings and on the pattern of inheritance. This diagnosis was confirmed by fibroblast typing, showing receptor deficient homozygosity, with 18% of normal high affinity LDL receptors (courtesy of Dr J L Goldstein, University of Texas Southwestern, Dallas, United States of America)

All the children were already on a low cholesterol, high P/S diet when their families were contacted for participation in the study. In some cases one or both of their parents were on or had been on a soybean protein based diet. On enrolment into the study children and parents were advised to follow their usual therapeutic diet as closely as possible This had a P/S ratio of about 1·6–1·8, with the following energy distribution. carbohydrates 55%, lipids 25%, and protein 20% (of which about 70% was of animal origin and 30% from vegetable sources); butter and cheese were excluded.

The children's plasma lipid concentrations were monitored after two (−2) and four weeks (0) of controlled low lipid regimen. At each interval plasma samples for lipid-lipoprotein determinations were collected. At time 0 all subjects (and their closest living relatives) received detailed instructions on the use of L-TVP, by following a short course (three days) of instructions for the preparation of the main recipes. The commercial product used was Cholsoy-L (relative percentage composition: protein 52·0, carbohydrate 23·6, fat 4·0, lecithin 6·0, fibre 3·5, minerals 6·5, and moisture 4·4).[6] By correctly assuming the prescribed diet about 90% of total proteins were derived from vegetable sources versus 10% of animal origin (mostly skimmed milk). Particular care was applied to the design of dietary programmes to allow normal development of the children without causing either undue increases or losses in weight.

At the −4, 0, +4 and, when possible, +8 week intervals the complete lipoprotein separation was carried out by preparative ultracentrifugation.[9] In four of the participants, all of whom were below the age of 6, the drawing of large blood samples was not considered appropriate, and lipoprotein distribution was determined, after selective precipitation of LDL and very low density lipoproteins,[10] by the use of the Friedewald formula.[11] Plasma cholesterol and triglyceride concentrations were determined at each visit by enzyme methodologies,[12 13] standardised, within each of the three laboratories, under the care of the World Health Organisation monitoring centre at Prague (Professor D Grafnetter).

Statistical analysis of the data was carried out by multiple paired comparisons with the Dunnett *t* test.[14]

Results

The experimental dietary plan was carefully explained to all children and their families, and all seemed capable of following it closely. All 16 children, in fact, successfully completed four weeks of treatment. After this, one child (case 5) withdrew for family reasons. There tended to be less compliance after the first month of dietary treatment. In spite of this, 12 children were still carefully following the regimen after both 12 and 18 weeks of treatment. At this point the study was considered to be complete and the data were analysed. At present, more than one year after the start of the study, eight of the children are still on a soybean diet plan, and two others are on a high P/S diet (around 1·6), with animal proteins being substituted by soy proteins in six meals each week.[15]

All subjects followed their regular pattern of weight increase during the study. In no case was there any unexpected decrease or pronounced increase (Table 1). The mean weight of the 12 subjects

Table 1 *Clinical characteristics of the participating subjects*

Case No	*Age (yrs)*	*Sex*	*Height (cm)*	*Centre*	*Total cholesterol (mg/dl) (−4 weeks)*	*Weight (kg)*	
						At −4 weeks	*At end of study (week)*
1	5	M	105	Mi	413	14·5	15 (18)
2	11	F	141	Mi	371	31·5	33 (18)
3	12	F	170	Mi	317	53	55 (18)
4	9	M	138	Mi	628	39	40 (12)
5	11	M	139	Mi	517	29·5	30 (4)
6	4	M	108	B	440	15·5	16·2 (12)
7	8	M	136	B	350	34	36·7 (18)
8	6	F	117	B	348	16·2	16·8 (18)
9	10	M	149	B	448	44	45 (18)
10	9	M	138	B	461	36	37·2 (18)
11	7	F	127	B	371	23	23·5 (18)
12	12	M	159	Me	280	45	48 (18)
13	12	F	158	Me	329	49	49·5 (12)
14	10	F	137	Me	266	33·5	34·5 (18)
15	8	M	132	Me	265	29	31 (18)
16	3	F	102	Me	200	19	21 (18)

Conversion traditional to SI units—Cholesterol 38·6 mg/dl = 1 mmol/l
Mi=Milan, B=Bologna, Me=Mendrisio

Table 2 *Plasma total cholesterol, triglycerides, and high density (HDL-chol) and low density (LDL-chol) cholesterol concentrations in all participating patients during the trial. All values are expressed in mg/dl and are mean (SD)*

	Weeks of trial					
	−4	*0*	*+4*	*+8*	*+12*	*+18*
No of subjects	16	16	16	15	12	12
Total cholesterol	375·8 (107·2)	360·3 (111·1)	291·5 (94·8)	278·4 (100·4)	287·2 (98·6)	287·3 (101·8)
Triglycerides	128·0 (42·6)	115·4 (45·8)	119·6 (47·1)	137·2 (67·9)	110·1 (34·4)	104·9 (28·4)
HDL-chol	36·4 (7·5)	35·6 (6·4)	36·8 (6·5)	35·3 (6·8)	36·1 (8·8)	37·0 (8·6)
LDL-chol	312·1 (102·1)	301·6 (106·4)	230·1 (87·5)	215·7 (94·7)	229·2 (97·1)	229·3 (98·7)

Conversion traditional to SI units—Cholesterol 38·6 mg/dl= 1 mmol/l, Triglycerides 88·6 mg/dl=1 mmol/l

completing 18 weeks of dietary treatment increased from 31·8 to 33·9 kg.

During the four pre-trial weeks (−4 to 0), no major changes in plasma lipid concentrations were detected. Mean (SD) plasma total cholesterol dropped from 375·8 (26·8) mg/dl to 360·3 (27·8) mg/dl at the end of the four weeks (not significant), possibly due to the improved compliance to the standard low lipid diet. Similarly, a small drop in triglyceridaemia was also noted (from mean (SD) 128·0 (10·6) to 115·4 (11·4) mg/dl, not significant). No specific changes were noted in high density lipoprotein (HDL) cholesterolaemia (Table 2).

After the start of the dietary treatment, the fall in cholesterolaemia was dramatic, even after two weeks of treatment. As four of the participating children did not report at the two week visit, data are given as the differences from baseline (0) at each interval (Figure). The mean (SD) reduction of plasma cholesterol concentration (12 children) was 56·0 (19·4) mg/dl after two weeks of L-TVP diet. All children reported at four weeks, when the mean cholesterol fall was 19·2% (p<0·001 *v* baseline). At this same interval, LDL-cholesterolaemia was reduced by 19·7% (also p<0·01 *v* baseline); triglyceridaemia had increased slightly (from mean (SD) 115·4 (45·8) to 119·6 (47·1) mg/dl, not significant) as had the HDL-cholesterolaemia (from 35·6 (6·4) mg/dl to 36·8 (6·5), not significant) In the 15 patients continuing treatment after eight weeks there was a further reduction of cholesterolaemia, which reached its minimum at −81·9 (11·1) mg/dl (−21·8%, p<0·0001 *v* their respective baseline). Little change was noted in triglyceridaemia and in HDL-cholesterol (Figure)

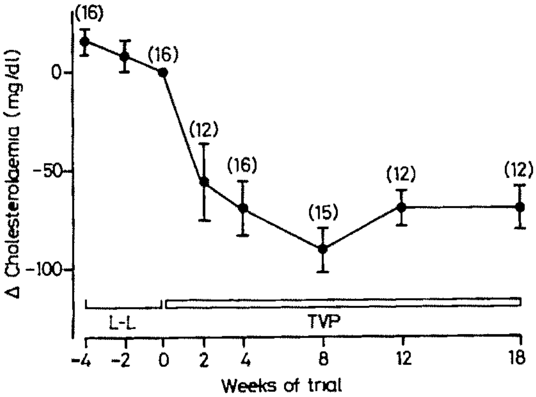

Figure *Mean (SD) changes in individual cholesterolaemias (△ mg/dl) in patients presenting at successive intervals during the study (numbers in parentheses= No of subjects) during the low-lipid (L-L) and soybean protein (TVP) diets.*

Conversion traditional to SI units—Cholesterol 38·6 mg/dl = 1 mmol/l

At the 12 and 18 week intervals the 12 remaining children showed a stabilisation of their serum cholesterol concentration, achieving a mean reduction around 70 mg/dl (−21·6% *v* their respective baselines, p<0·001 in both cases). At these intervals no further significant changes were recorded for triglyceridaemia, whereas a further small rise in HDL-cholesterol was recorded (Table 2).

Discussion

The effect of the addition or subtraction of different dietary nutrients on cholesterolaemia has been repeatedly examined in both normal subjects and patients with hypercholesterolaemia.[16] Specific formulas have been proposed to evaluate quantitatively the effect of varying the P/S ratio or the dietary cholesterol intake, or both.[17 18] More recently, it has been suggested that the P/S ratio may be of less importance when subjects consume a diet with a fairly low (less than 30%) fat content.[19]

Compared with the wealth of knowledge related to adult hypercholesterolaemia, little is known on the specific sensitivity of children to dietary changes. Apparently, both infants[20] and young children[3] seem to be remarkably sensitive to dietary cholesterol and fat restriction, generally showing dramatic plasma cholesterol reductions on shifting from a diet of ≥400 mg/day cholesterol to a diet with <150 mg/day The effects are, however, far less striking after children with hypercholesterolaemia reach 6 years of age Rose *et al* detected a 20% reduction of serum cholesterol in only eight of 16 children with type II disease treated for one year with a low cholesterol, high P/S diet; no substantial change was found in the other eight. More recently, Fernandes *et al* tested a virtually cholesterol free, high linoleic acid vegetarian diet, with 39% of energy from vegetable protein against 33% in the reference low lipid diet, in children with type II disease.[5] The mean cholesterol reduction induced in these 39 children (4 to 14 years of age) was around 10%; HDL-cholesterol and apo AI decreased by 4%.[5] In a study with different objectives MacLean *et al* noted that in malnourished children animal proteins (casein) led to 36% higher cholesterolaemias compared with vegetable proteins (wheat).[21]

Based on our large clinical experience with the total substitution of animal proteins with TVP from soybean in the treatment of adult patients with type II hypercholesterolaemia,[4 6] this diet was administered to a group of 16 children with an inherited form of hypercholesterolaemia Some came from families where the disease had exerted an appreciable impact on the cardiovascular morbidity and mortality. Another incentive to this study was the recent observation, by one of our groups, of an up regulatory effect of this diet on liver lipoprotein receptors, down regulated by dietary cholesterol[22] In view of the clear importance of an impaired receptorial regulation in many of these children, this type of diet seemed capable of providing a satisfactory alternative to effective, but at times poorly tolerated,[23] treatment with drugs

The described results show that children respond to the dietary change in a more or less similar way to adults. Unexpectedly, we found it difficult to maintain many of these children on a strict regimen for a prolonged period. We hoped that children, less exposed to the habitual consumption of animal protein compared with adults, would accept the new regimen better. This was not the case, possibly because of the constant exposure to highly publicised food items, as well as to the school environment. One of the children (case 4), with a homozygous receptor deficient disease, was treated, however, with the regimen during admission to hospital; after just four weeks of a strictly controlled diet he presented with a plasma cholesterol reduction of close to 30%. Greater sensitivity of children compared with adults cannot thus be excluded. Moreover, more than half of the children have continued the regimen, either on a total basis or on partial substitution,[15] for over a year.

The cholesterol reduction seems to be limited to changes in LDL concentrations. In contrast to the experience of Fernandes *et al*,[5] we failed to note any drop in HDL-cholesterol. Indeed, to some extent similar to our previous experience with adult patients with type II hypercholesterolaemia treated with the new TVP regimen containing 6% lecithin,[6] we noted a slight trend to increase in HDLs In the other study only patients with a very low HDL-cholesterol responded with a significant increase when placed on the new diet.[6] Also because of the fairly small number of children with very low HDL-cholesterol in this study we could not show the presence of a similar trend in our patients

In conclusion, it seems that the soybean diet regimen can provide a safe and effective dietary treatment for children with type II hypercholesterolaemia, even with familial conditions The potential of this regimen to reduce the incidence and severity of arterial complications needs to be evaluated further

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1992 April 7–11
1993 April 19–23 (provisional)
1994 April 11–15 (provisional)

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The inter-regional epidemiological study of childhood cancer (IRESCC)*: a case control study of aetiological factors in leukaemia and lymphoma

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SUMMARY The inter-regional epidemiological study of childhood cancer analysed data on 234 children diagnosed with leukaemia or lymphoma and 468 controls matched for age and sex. A wide range of potential risk factors was examined, including prenatal exposure to *x* rays, maternal drug ingestion and smoking, child's medical history, and parental medical conditions and occupation. Calculations were completed for leukaemia or lymphoma and diagnostic subgroups, as defined by laboratory confirmed cell type. In utero exposure to narcotic analgesics was weakly associated with leukaemia or lymphoma but no other antenatal factors gave significant risks. New associations were identified for skin diseases in both parents and congenital abnormalities in the mothers of children with leukaemia. For past medical conditions in the child, viral disease occurring under 6 months of age increased the risk for acute lymphoblastic leukaemia. Fewer children in the leukaemia or lymphoma group had been immunised compared with the control groups. Case children diagnosed over the age of 9 years were more likely than controls to have had four or more previous episodes of illness. Overall, these results indicate that prenatal factors may be less important than postnatal or genetic influences in the development of leukaemia or lymphoma in children.

In the United Kingdom data have suggested a rise in the incidence of childhood leukaemia.[1 2] The reasons for this increase remain obscure, in parallel with the failure of epidemiological studies to detect any major risk factors for childhood leukaemia or lymphoma. Advances in immunophenotyping of haematologic malignancies now permit the identification of distinct subtypes of diseases once thought to be single entities Hence aetiological investigation of accurately classified disease phenotypes can be accomplished. As yet few epidemiological studies have incorporated this approach, particularly for childhood reticuloendothelial neoplasms.

The inter-regional epidemiological study of childhood cancer (IRESCC), a collaborative case control study, gathered a wide range of information from parents of 555 children diagnosed with childhood cancer and 1110 control children. The aim of this paper is to present the systematic evaluation of aetiological factors relating to the 234 cases of childhood leukaemia or lymphoma.

Methods

The study was conducted in three regional health authorities—Yorkshire, West Midlands, and North West. Cases of childhood malignancy were ascertained within these defined geographical areas from January 1980 to January 1983. Details of the case control methodology as applied to this study are described elsewhere.[3] A total of 234 case children

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*IRESCC Group the authors and Dr C C Bailey, Dr A H Cameron, Dr R H A Campbell, Dr S C Cartwright, Mr J J Corkery, Dr D Deakin, Mr P Gornall, Dr H B Marsden, Dr P H Morris-Jones, Dr D Pearson, Mr R Swindell, and Mrs J Williams (under 15 years) diagnosed with leukaemia or lymphoma were included and their parents interviewed with a standard questionnaire. Each case child was matched for age and sex with two healthy control children selected from admissions to hospital and general practitioner lists. Identical information was gathered from the parents of these control children as had been gathered from the parents of the children with leukaemia or lymphoma. Questions asked for details of the index antenatal period (illness, investigations, drug ingestion, complications, smoking, and alcohol consumption), medical history of the child, parents, and other family members, and parental occupation and smoking habits. Additional data were abstracted from medical notes In particular, efforts were made to see relevant obstetric notes for every case and control mother interviewed. For both parents and child, diseases and conditions not related to pregnancy were coded according to the *International Classification of Diseases*,[4] apart from gynaecological problems, which had unique IRESCC codes. Social class was assessed according to the father's occupation at the time of the child's birth.[5]

An extensive range of risk factors was investigated for any possible association with childhood leukaemia or lymphoma. Preliminary tables for case control comparisons were produced using SPSS version X [6] Statistical analysis of cases versus pooled (hospital and general practitioner) controls was completed on a Hewlett Packard 41CV programmable calculator using the programs of Rothman and Boice.[7] Relative risks were produced by the Mantel-Haenzsel method, with tests based on 95% confidence intervals and two tail p values χ^2 and t tests were used when appropriate on certain variables.

Results

The distribution for sex and age at diagnosis of the 234 children with leukaemia or lymphoma who were interviewed is shown in Table 1. They were not the complete set of incident cases from the three study regions because certain exclusions were made[3] for pragmatic reasons

All 234 children with leukaemia or lymphoma had cytologically or histologically confirmed diagnoses. Of the 171 children with leukaemia, 148 were typed as acute lymphoblastic leukaemia, with common acute lymphoblastic leukaemia being confirmed by Professor M F Greaves in 78 patients. The 'other acute lymphoblastic leukaemia' group included diagnoses of uncertain cell origin, T cell, B cell, and null cell acute lymphoblastic leukaemia and 24 cases not submitted for cell typing, as detailed in Table 1. Most of the other leukaemias were of myeloid origin. The lymphomas (63 cases) were equally distributed between Hodgkin's disease (32 cases) and non-Hodgkin's lymphoma (31). The rationale for categorising the leukaemia or lymphoma was based on the hypothesis that varying cell types of disease may have differing aetiologies and laboratory confirmation of individual phenotypes permits investigation of homogeneous subgroups. Insufficient numbers necessitated grouping some cell types, though most of the untested cases of acute lymphoblastic leukaemia were probably of the common null cell type.

Table 1 *Incidence of leukaemia/lymphoma cell type by sex (M=male, F=female) for age at diagnosis*

Disease subtype	*Age at diagnosis*						*Total*
	Under 2 years		*2–8 years*		*9–14 years*		
	M	*F*	*M*	*F*	*M*	*F*	
Common acute lymphoblastic leukaemia	5	1	32	26	9	5	78
'Other' acute lymphoblastic leukaemia*	2	7	24	19	8	10	70
Myeloid leukaemias†	1	1	6	6	5	4	23
Total leukaemias	8	9	62	51	22	19	171
Hodgkin's disease	0	0	10	2	15	5	32
Non-Hodgkin's lymphoma	1	0	13	5	8	4	31
Total lymphomas	1	0	23	7	23	9	63
Total leukaemia/lymphoma	9	9	85	58	45	28	234

*Includes cases untested for cell type (24), T cell (10), B cell (two), and null cell acute lymphoblastic leukaemia (eight), and uncertain cell type (26)
†Includes acute myeloid leukaemia (18), chronic myeloid leukaemia (two), acute promyelocytic leukaemia (one), erythroleukaemia (one), and megakaryocytic leukaemia (one)

For many of the potential risk factors investigated, no significant case control differences emerged either for major diagnostic groups (leukaemia or lymphoma, leukaemias, and lymphomas) or smaller sized subgroups. Table 2 lists the factors examined that fell into this category, detailing the type of comparisons made. None of the relative risks were greater than 2 or reached significance at the 5% level.

Pregnancy and related events. Fetal exposure to potential carcinogens was investigated by close examination of the relevant antenatal period, using both interview reports and medical records No obstetric notes were available, from either the general practitioner or the hospital, for a very small number of mothers—three cases of leukaemia or lymphoma and six general practitioner and three hospital controls. Antenatal factors apparently unrelated to the subsequent development of leukaemia or lymphoma are shown in Table 2. Birth weight was similar for cases and controls in the pooled diagnostic group (leukaemia and lymphoma) but for those in the lymphoma group the mean birth weight of cases and controls was significantly different The case babies were lighter than their matched controls (mean birth weight for cases 3260 g and for controls 3433 g, p=0·05, *t* test). This was accounted for by the babies with non-Hodgkin's lymphoma (cases 3194 g, controls 3437 g, p=0·05, *t* test).

Risks to the fetus of maternal drug ingestion were calculated, grouping drugs according to their pharmacological action Table 3 shows the absence of any major transplacental carcinogenic effect for most drug groups apart from narcotic analgesics ingested in pregnancy and barbiturates taken during labour. The significant relative risk of 8·3 for the group with leukaemia or lymphoma with reported ingestion of narcotic analgesics was due to the leukaemia subgroup (seven cases (seven acute, none myeloid), one general practitioner control, one hospital control; relative risk=7·3, 95% confidence intervals 1·9, 28·3; p<0·01), with medically prescribed narcotic analgesics approaching significance.

Table 2 *Factors that failed to show any major positive* associations with childhood leukaemia or lymphoma*

Pregnancy and related events
Interval between stopping oral contraception and conception (no gap or <3 months)†
Type of antenatal care (hospital or general practitioner practice, or both)
Amniocentesis examination
General anaesthetic
Alcohol consumption
Duration of gestation
Type of delivery (normal, breech, assisted, or caesarean)
Place of delivery (home or hospital)
Maternal smoking (1–20 cigarettes a day, 21 or more cigarettes a day)
Infections during pregnancy (influenza, urinary tract infection)
Toxaemia
Threatened miscarriage
Ultrasound examinations

Birth and neonatal experiences
Apgar score at birth (<5 *v* rest)
Breast fed
Length at birth
Birth weight‡

Family factors
Maternal age (<24 years, <20 years, <40 years)
Paternal age (<20 years, <40 years)
Birth order (rank 1 *v* rest)
Sibship size (five or more sibs), excluding 1/2 sibs
Father's social class (I, II, IIIN *v* IIIM, IV, V)

Other factors
Fathers smoking (1–20 cigarettes a day 21 or more cigarettes a day)
Exposure to pets (for example, all mammals, cats birds)

*That is, relative risks <2 and non-significant statistical tests
†Bracketed information indicates comparisons used in the analysis, otherwise nominal binary groups were used
‡See text

Table 3 *Drugs ingested during index pregnancy and labour*

Pharmacological groups of drugs with non-significant relative risks

Drug group	*Estimated relative risk for leukaemias/lymphomas*	
	Reported at interview	*Medically recorded*
Analgesics	0·9	1·3
Antibiotics	1·0	1·0
Antifungals	0·6	0·7
Antihistamines	1·3	1·1
Barbiturates (pregnancy only)	1·0	1·0
Benzodiazepines	0·7	0·9
Diuretics	1·0	1·4
Hormones	0·9	0·7
Hormone confirmation of pregnancy	0·8	1·2
Topical steroids	1·0	0·6
Phenothiazines (major tranquilisers)	2·0	1·5

Drug groups with significant associations

Drug group	*Diagnostic group (No of cases)*	*Reported at interview or medically recorded*	*Relative risk*	*95% Confidence intervals*	*p Value*
Narcotic analgesics (during pregnancy)	Leukaemia/lymphoma (234)	Reported at interview	8·3	2·2, 30·7	<0·01
		Medically recorded	1·4	0·7 2·7	0·29
	Leukaemias (171)	Reported at interview	7·3	1·9, 28·3	<0·01
		Medically recorded	2·0	1·0, 4·0	0·06
Barbiturates (in labour)	Leukaemia/lymphoma (234)	Medically recorded	5·5	1·7, 18·1	<0·01
	Leukaemias (171)	Medically recorded	3·0	0·6 16·9	0·20
	Lymphomas (63)	Medically recorded	10·8	1·8 63·2	<0·01

For medically recorded ingestion of narcotic analgesics 15 case children exposed in utero were diagnosed, seven with common null cell acute lymphoblastic leukaemia, seven with acute lymphoblastic leukaemia, and one with myeloid leukaemia. Dextropropoxyphene hydrochloride (Distalgesic) was the commonest narcotic analgesic used and similar reasons were given by case and control mothers for its usage. Drugs administered during labour were recorded only from medical notes. A significantly raised relative risk of 5·5 for barbiturates in the group with leukaemia or lymphoma was due to excessive numbers in the lymphoma subgroup (five cases (two Hodgkin's disease, three non-Hodgkin's lymphoma), one general practitioner control, no hospital control; relative risk=10·8, 95% confidence intervals 1·8, 63·2; p<0·01).

In utero exposure to *x* rays was analysed using data from medical notes, counting direct fetal exposure from abdominal/pelvic *x* rays, and using pelvimetry. Ninety five per cent of pelvic films taken were in the third trimester for cases and controls Reasons given for the prescription of giving *x* rays included suspicion of multiple pregnancy, fetal abnormality or presentation, 'checking dates'/determining maturity, and a single instance of 'confirmation of engaged fetal head'. The relative risks for pelvic radiography were all greater than unity but not significant. Stratifying the 'pelvic' group by age at diagnosis gave seven cases, three general practitioner controls, and two hospital controls exposed in the group with leukaemia or lymphoma diagnosed under 2 years of age (relative risk=3·4, 95% confidence intervals 0·9, 12 9; p=0·07). The referent category of mothers had received no *x* rays of any type—for example, chest *x* rays. No risk for any other age reached significance.

Illnesses in parents. The medical history of the index child's mother and, where possible, father was recorded at interview. Attempts were made to confirm medically congenital abnormalities, cancers, and chronic diseases. The medical histories of the fathers and mothers of the index children did not differ significantly from those of the controls with regard to musculoskeletal and connective tissue disorders (ICD9 710–739), central nervous system disorders (ICD9 320–349), mental disorders (ICD9 290–319), or respiratory system diseases (ICD9 460–519). For skin diseases (ICD9 680–709), however, significant relative risks were present within the major diagnostic groups for both parents (Table 4). There was only one case of both parents of a case child having a skin condition. Medically recorded data showed a case excess for the leukaemias (fathers: eight cases, three general practitioner

Table 4 *Maternal and paternal illnesses linked to childhood leukaemia or lymphoma*

Condition (ICD9)	*Diagnostic group (No of cases)*	*Reported at interview or medically recorded*	*Father*		*p Value*	*Mother*		*p Value*
			Relative risk	*95% Confidence intervals*		*Relative risk*	*95% Confidence intervals*	
Skin diseases (680–709)	Leukaemia/lymphoma (234)	Reported at interview	1·3	0·8, 2·0	0·32	1·1	0·7, 1·7	0·70
		Medically recorded	2·8	1·2, 6·9	0·02*	1·8	1·0, 3·4	0·07
	Leukaemias (171)	Reported at interview	1·4	0·8, 2·3	0·29	1·2	0·7, 2·0	0·43
		Medically recorded	4·2	1·4, 12·8	0·01*	2·3	1·1, 4·7	0·03*
	Common acute lymphoblastic leukaemia (78)	Reported at interview	1·4	0·6, 3·2	0·46	1·5	0·7, 3·5	0·30
		Medically recorded	13·0	2·4, 67·9	<0·01*	2·1	0·6, 7·2	0·25
	'Other' acute lymphoblastic leukaemias (70)	Reported at interview	1·7	0·8, 3·6	0·18	1·2	0·5, 2·5	0·61
		Medically recorded	4·1	0·4, 38·5	0·21	2·9	1·0, 8·3	0·05*
	Lymphomas (63)	Reported at interview	1·1	0·4, 2·7	0·88	0·7	0·3, 2·0	0·52
		Medically recorded	1·5	0·3, 7·0	0·59	1·0	—	—
Congenital anomalies (740–759)	Leukaemias/lymphomas (234)	Reported at interview	Nil significant			1·9	1·0, 3·9	0·07
		Medically recorded				3·3	1·1, 9·6	0·03*
	Leukaemias (171)	Reported at interview				3·0	1·3, 7·0	0·01*
		Medically recorded				4·2	1·4, 12·8	0·01

*Significant at 5% level

controls, one hospital control; mothers: 15 cases, four general practitioner controls, 10 hospital controls), accounted for by the common null cell and other acute lymphoblastic leukaemia subgroups in the fathers and mothers, respectively. Confining the analysis to eczema/dermatitis conditions (ICD9 690–698) resulted in a non-significant case excess for both parents in the leukaemia or lymphoma group (fathers: five cases, four general practitioner controls, one hospital control; mothers: 11 cases, four general practitioner controls, 12 hospital controls). Congenital anomalies (ICD9 740–759) occurred more often in case mothers, particularly those with children with leukaemia (interview reports: 13 cases, two general practitioner controls, seven hospital controls; medical records: eight cases, one general practitioner control, three hospital controls). Estimated relative risks are shown in Table 4. Much of the excess was due to ICD9 757·9—mainly non-specific birthmarks. Case control comparisons for all diagnostic groups gave no increased risk for the following gynaecological conditions occurring either before or after the index pregnancy. fibroids, cysts and polyps of the genital tract, infertility, and menorrhagia.

Child's medical history. Details of congenital anomalies, chronic disease, and childhood illnesses were obtained for the index child, but medical confirmation was sought routinely only for major congenital abnormalities and chronic diseases. Case control comparisons were made for respiratory system diseases (ICD9 460–519), central nervous system disorders (ICD9 320–349), and skin diseases (ICD9 680–709), but large numbers of reported conditions were of a non-specific nature. No case control differences were evident for these conditions.

Viral diseases (ICD9 045–079, 408), comprising chickenpox, rubella, measles, mumps, viral meningitis, and viral influenza, were recorded at interview if the episodes occurred when the child was under 6 months of age. In the group with leukaemia or lymphoma a significantly increased number of case children were noted to have had viral illnesses (Table 5). This was accounted for particularly by the common null cell acute lymphoblastic leukaemia and lymphoma subgroups (Table 6). No significant differences were present for respiratory system disorders or skin diseases diagnosed under 6 months of age. Children with viral disease in the six months before diagnosis were excluded from analysis. Reports of early viral diseases were proportionately distributed between the three regions that contributed data.

Analysis of the total number of episodes of illness for each child revealed that case children had an increased frequency of diseases compared with controls. Comparing a history of three or less instances with four or more, risks approached and reached significance for reported and medically recorded data, respectively, in the group with leukaemia or lymphoma (Table 5). The children with leukaemia accounted for the reported excess, with the children with lymphoma showing a significant risk for medically recorded illness due to three cases of non-Hodgkin's lymphoma and no controls. On stratification by age at diagnosis (under 2 years, 2–8 years, and 9–14 years) a significant excess was shown only in the 9–14 age group.

Table 5 also shows that for the group with leukaemia or lymphoma and the leukaemia subgroup, more case than control children failed to receive their usual vaccinations (leukaemia or lymphoma: six cases, no general practitioner

Table 5 *Risk factors in index child's medical history*

Risk factor	*Diagnostic group (No of cases)*	*Relative risk*	*95% Confidence intervals*	*p Value*	*Reported at interview or medically recorded*
Viral disease* (ICD9 045–079, 480) under 6 months of age	Leukaemia/lymphoma (234)	4·1	1·5, 11·3	<0·01	Reported at interview
Immunisations†	Leukaemia/lymphoma (234)	0·3	0·1, 1·1	0·07	Reported at interview
	Leukaemias (171)	0·2	0·1, 0·9	0·03	Reported at interview
	Myeloid leukaemias (23)	0·1	0·0, 1·0	0·05	Reported at interview
	Lymphomas (63)	1·0	0·1, 11·5	0·99	Reported at interview
No of episodes of illness per child‡ (<4 v ≥4)	Leukaemia/lymphoma (234)	1·6	0·1 2·7	0·06	Reported at interview
		2·4	1·1 4·9	0·02	Medically recorded
	Leukaemias (171)	1·9	1·0, 3·4	0·04	Reported at interview
		1·6	0·5, 5·0	0·46	Medically recorded
	Lymphomas (63)	1·1	0·4, 3·1	0·81	Reported at interview
		5·7	1·2, 27·1	0·03	Medically recorded

*Excludes cases with viral diseases in the six months before diagnosis (and for controls pseudodiagnosis)

†Excludes cases diagnosed under 1 year of age

Exposed children are those given one or more of tetanus, diphtheria, whooping cough, smallpox, polio measles or triple vaccination

‡Includes all ICD9 coded illness, excluding congenital anomalies

Study protocol did not attempt to confirm viral disease and immunisations

Table 6 *Viral diseases occurring under 6 months of age*

Case diagnosis	*Cell type*	*Disease*	*Time interval (disease to diagnosis) (years)*
Cases			
Acute lymphoblastic leukaemia	Common	Chickenpox	5
Acute lymphoblastic leukaemia	Common	Chickenpox	4
Acute lymphoblastic leukaemia	Common	Viral meningitis	2 5
Acute lymphoblastic leukaemia	Common	Rubella	2·5
Acute lymphoblastic leukaemia	'Other'	Measles	5 5
Myeloid leukaemia	—	Rubella	14 5
Non-Hodgkin's lymphoma	Not known	Viral influenza	6
Non-Hodgkin's lymphoma	Not known	Measles	7 3
Non-Hodgkin's lymphoma	Not known	'Bronchial' virus Rubella	4 5
Hodgkin's disease	—	Mumps	13
General practitioner controls			
Acute lymphoblastic leukaemia	Common	Measles	4 5
Hospital control			
Acute lymphoblastic leukaemia	Common	Rubella	2·5
Acute lymphoblastic leukaemia	'Other'	Measles	10
Acute lymphoblastic leukaemia	'Other'	Chickenpox Measles	11
Acute lymphoblastic leukaemia	Untested	Viral infection (unspecified)	3·5

Table 7 *Parental occupation*

Mother

No associations with textile or clothing workers, any factory related occupation, clerical or sales workers, electronic/electrical workers, or professional/technical workers

Father

Occupations lacking major associations	*Possible risk occupations*
Miners/quarrymen	*Furnace/forge/foundry workers*
Gas, coke, and chemical workers	Leukaemia/lymphoma relative risk 4 8, 95% confidence intervals 1 4 16 5
Electrical/electronic workers	Lymphomas 4 cases, 0 controls
Engineering	
Woodworkers	*Textile workers*
Paper and printing workers	Lymphomas relative risk 8 5, 95% confidence intervals 1 3, 55 1
Painters and decorators	Hodgkin's disease 2 cases, 1 control
Drivers	Non-Hodgkin's lymphoma 2 cases, 0 controls
Transport and communication workers	
Service, sport, and recreation workers	*Construction workers*
Administrators and managers	Common acute lymphoblastic leukaemia relative risk 2 9, 95% confidence intervals 1 2, 7 5
Professional and technical workers	
Armed forces	
Farmers, foresters, and fishermen	
Food, drink, and tobacco workers	
Sales workers	

controls, four hospital controls; leukaemia: five cases, no general practitioner controls, two hospital controls). Children diagnosed under 1 year of age were excluded from these calculations

Parental occupation. No maternal occupation, with sufficient numbers to allow analysis, was associated with any major risk of childhood reticuloendothelial malignancy. Table 7 shows that there was a case excess of fathers who were furnace/forge and foundry workers, textile workers, and construction workers for certain diagnostic subgroups.

Discussion

Children diagnosed with leukaemia or lymphoma included in the IRESCC have previously been shown to be representative of this disease group within the UK.[3] The case distribution shows a typical age peak in the 2–8 year olds for acute lymphoblastic leukaemia, an absence of Hodgkin's disease in the under 2s, and overall male predominance, particularly in the lymphomas subgroup. Roughly half of the acute lymphoblastic leukaemia subgroup were immunologically subtyped as confirmed common null cell type. This aspect of our investigation was an important one, linking laboratory evidence of distinct disease entities with epidemiological methods investigating aetiological factors, an approach recommended in the light of recent developments in laboratory techniques.[8]

A variety of possible risk factors for leukaemia or lymphoma in children have previously been investigated, but few clear cut associations have emerged, an exception being in utero exposure to x rays.[9 10] Our study results support these findings, specifically showing an increased risk (relative risk 3·4) for leukaemia or lymphoma diagnosed under 2 years of age Reduction of significance in the present analysis compared with previous data[11] can be explained, firstly, by differences in the assignment of controls. In the original letter controls with histiocytosis X were not excluded from the stratified analysis. Secondly, the total number of cases with leukaemia or lymphoma was reduced from 245 to 234 by removal of the nine cases with histiocytosis X (six diagnosed under 2 years) and two instances where diagnostic review resulted in recategorisation from the group with leukaemia or lymphoma. The results expressed in this x ray analysis follow the stratified format adopted throughout the paper, and although the relative risk for x rays is still high for the group with leukaemia or lymphoma, the smaller numbers in the cells fail to achieve significance

Any drug ingested during pregnancy has the potential to cross the placenta, presenting a hazard to the developing fetus. Firm data on carcinogenic risks of antenatal drug use, particularly with reference to childhood leukaemia or lymphoma, are sparse. Sedatives and hormones taken during pregnancy have been claimed to convey increased risk of leukaemia[12] and all childhood cancers,[13] but this was not corroborated by our analysis. Direct comparison between studies is difficult as the systematic evaluation of pharmacological drug groups in our study used carefully defined categories[14] not evident elsewhere in the published reports. For example, it is difficult to understand the term 'sedative'.[12] An excess of case mothers took narcotic or opioid analgesics (mostly Distalgesic), an association reaching significance only for the information given at interview and not found for 'euphoriant analgesics' in another study.[15] Ingestion of the drug was not allied to any particular condition, suggesting that the drug accounts for the association. Over reporting by case mothers could explain our observation but seems unlikely in the absence of positive links for other drug groups A single significant association among multiple comparisons, however, may well be fortuitous. A stronger link can only be established by further testing of this new finding.

According to medical records, barbiturates were administered during labour to more mothers of children with lymphoma than to the mothers of the matched controls. This association was lost when barbiturates at any time during the index pregnancy were examined; making them unlikely transplacental carcinogens.

This study gathered detailed information on the medical history of both parents. Analysis of ICD9 coded groups showed no case excesses in any category except for mothers and fathers with skin diseases, where the association was most prominent for acute lymphoblastic leukaemia. No particular condition was more prevalent for either parent and it is of interest that maternal and paternal links existed. These findings are unique and require corroboration from other independent studies. A Yorkshire case control study of adult leukaemia and lymphoma found a case excess of skin disease in the patients themselves.[16] We are unable to hypothesise a causal explanation, although skin diseases may well be markers of some other associated inherited factor, such as a malfunctioning immune system. The frequency of congenital anomalies in the parents of children with leukaemia or lymphoma has not been previously reported and the significant excess of mothers, mainly in the group with leukaemia, is of interest but as yet inexplicable.

A striking finding from our data on the leukaemia or lymphoma group was the significant relative risk for contracting a viral disease under the age of 6 months. The development of leukaemia or lymphoma has long been linked to malfunctioning immunity, and the maturing neonatal immune system requires time to develop active immunity in response to antigenic stimulation, making early exposure to disease particularly relevant. Based on this idea we recorded all instances of infections under the age of 6 months. No case excess was found for any disease occurring after 6 months and the significance of viral exposure at a younger age was limited to the pooled leukaemia or lymphoma group. The latent period between viral exposure and malignancy ranged from 2·5 to 5·5 years for cases of acute lymphoblastic leukaemia; numbers in other groups were small, ranging from 4·5 to 14·5 years. For acute lymphoblastic leukaemia, the minimum gap of 2·5 years makes it unlikely that the viral disease was expressed due to intrinsic immunosuppression in the preclinical phase of malignancy, which Stewart estimated as one year.[17] The rarity of both leukaemia or lymphoma in childhood and viral disease under 6 months means that our risk estimates are based on small numbers. In contrast, one study has shown that children with leukaemia have fewer infections in the first year of life.[18] Further conflict is apparent from our own data, where an excess of case children were not immunised Small numbers make this apparent protective effect of immunisation an unreliable observation, although another recent and larger study had similar findings.[19] The role the immune system plays in haematopoietic malignancies is unclear, and our association with early viral disease may be independent of immune regulation and effect malignant transformation through another route.

The association between childhood leukaemia or lymphoma and increased episodes of previous illness could be explained by over reporting by mothers of cases or under reporting by control mothers. This, however, seems unlikely because the case control differences are present for both interview reports and medically recorded conditions. Also the fact that the effect was strongest in the 9–14 age group is evidence against over reporting by case mothers. It was impossible in this study to assign the excess to one particular disease group or to determine whether any conditions were related to a susceptible period before diagnosis.

Parental occupation is a commonly investigated link with childhood cancer. A recent review article clearly showed the conflicting nature of results from previous studies.[20] Our findings gave no indication of any risk occupations for the mother during the index pregnancy or before conception. For leukaemia, other studies have shown increased risk in association with hydrocarbon and chemical related occupational exposure during pregnancy[21] and with mothers who were pharmacists.[22] Hydrocarbon related paternal occupations have been positively[23–25] or equivocally[26–29] linked to childhood leukaemia or lymphoma. Our finding of furnace/forge and foundry workers as a risk occupation for the group with leukaemia or lymphoma was accounted for by the lymphoma subgroup. Measurements of potential carcinogenic exposure within a working environment are generally unevaluable, and biologically plausible links with childhood cancer may be tenuous. Textile workers and construction workers were weakly linked to lymphomas and common null cell acute lymphoblastic leukaemia, respectively, relations that are also unsupported in previous publications.

Of broader interest is the documented increase in risk for children with leukaemia or lymphoma of parents in higher social classes.[28 30 31] although our study and some others have failed to provide corroboration.[29 1] World wide, childhood acute lymphoblastic leukaemia seems to be a disease associated with improved living standards,[32] although comparisons are relative and smaller socioeconomic differences will exist within the UK population

Overall, results from this major epidemiological study have shown few aetiological factors positively linked to childhood leukaemia or lymphoma. The definition of diagnostic subgroups by cell type failed to clarify the picture or identify particular risk factors or susceptible children, but small numbers were a significant disadvantage in the more detailed analyses. The general lack of associations for prenatal factors suggests that postnatal exposures may possibly be of greater importance in the aetiology of childhood leukaemia or lymphoma. Possible genetic influences have not been explored in this paper but will be addressed in more detail in the future.

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Prognosis in severe Guillain-Barré syndrome

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SUMMARY Recent studies of Guillain-Barré syndrome in adults have shown that the requirement for assisted ventilation correlates closely with a poor outcome, and the need for ventilation is now being used as an indication for plasmapheresis. As comparable studies in children have not been performed we reviewed our experience of patients who had Guillain-Barré syndrome severe enough to require assisted ventilation. In a group of 11 children two died in the acute stage of the illness and nine made an excellent recovery. It would seem that the need for mechanical ventilation is not necessarily a bad prognostic factor for neurological recovery in children.

Guillain-Barré syndrome affects at least 1·7 per 100 000 of the population every year.[1] This inflammatory demyelinating disease of peripheral nerves is often thought to have a benign prognosis, but roughly 7% of adult patients die and a further 7–22% suffer residual disability.[2–4] No comparable figures are available for Guillain-Barré syndrome in children, although there is some evidence that severe residual deficits are rare and that the natural history of the disease in childhood may be different.[5]

There have been several recent multicentre studies on the treatment of Guillain-Barré syndrome in adults,[2 6 7] and these have shown that steroids are ineffective[6 7] but that plasmapheresis is beneficial both in shortening the duration of acute illness and improving neurological outcome [2 8] Reservations have been expressed, however, about using plasmapheresis indiscriminately in a disease where most patients will recover spontaneously and where the technique itself is not without hazard [9 10] Selection for treatment of those patients who would otherwise do badly has thus been advocated.[9 10] Winer *et al* in a recent retrospective study of 71 adults have attempted to identify such patients.[11] In their study those patients who required assisted ventilation were shown to be the most likely to have an incomplete neurological recovery As a result of these recent findings we have reviewed our experience, with particular reference to outcome, of those children with severe demyelinating polyneuropathy who required ventilation.

Patients and methods

During the seven years 1977–84, 11 children with demyelinating polyneuropathy required assisted ventilation at our hospital There were six boys and five girls in the series, aged from 3 to 13 years. Details of the acute illness were obtained from case notes. The survivors were reviewed between 15 months and six years after the onset of illness At review, a questionnaire was completed in which details of school performance, duration of rehabilitation, functional neurological deficit, and subsequent respiratory problems were sought. The children were weighed, measured, examined, and given a detailed physiotherapy assessment, which included charting of muscle strength. Pulmonary function tests were performed. Lung volumes were assessed by helium dilution technique and full body platysmography. Maximum expiratory flow volume curves were recorded by Fleisch pneumotachograph and from these the forced vital capacity, forced expiratory volume in one second, and volume maximum 25% vital capacity were calculated. Peak expiratory and inspiratory mouth pressures (an indication of respiratory muscle power) were measured. All children had diaphragmatic movement assessed by radiological screening.

Results

Acute illness. Nine of the children presented with a history and clinical findings of classical Guillain-Barré syndrome and the other two children (cases 10 and 11) showed the more protracted natural history of chronic, progressive/relapsing polyneuropathy (Table 1)

At presentation all the children had cerebrospinal fluid findings compatible with a diagnosis of demyelinating polyneuropathy, and in those five chil-

Table 1 *Clinical features of acute Guillain-Barré syndrome in 11 children. Cases 10 and 11 had chronic relapsing polyneuropathy*

	Case No										
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
Cranial nerve involvement	+			+		+		+		+	+
Encephalopathy	+			+	+			+	+		
Hypertension		+	+		+	+					
Cardiac arrest		x2		1	1					1	1
Treatment					Steroids			Steroids	Steroids	Steroids, immunosuppressants, plasmapheresis	Steroids immunosuppressants plasmapheresis
Outcome									Death		Death

dren in whom nerve conduction studies were performed there was evidence of slowing of conduction Seven of the 11 children had abnormal chest x ray films at admission (Table 2).

Five children were being ventilated on admission to our unit and the others were referred because respiratory failure was thought to be imminent. Eight of the children required ventilation within two weeks of onset of illness, and the duration of ventilation ranged from three days to five weeks. Five children were treated with steroids for at least part of their illness, although no standardised regimen was employed, and the two children with the relapsing form of the illness were treated with immunosuppressants and plasmapheresis as well. Two children died, one with the acute illness and the other with the progressive relapsing form of the disease

Follow up assessment. The nine survivors all had normal pulmonary function tests at review, apart from one boy who had developed asthma and had a mild obstructive defect. Respiratory muscle function was unimpaired in all the children

All the children had returned to normal school after their illness On examination, seven of the nine children had made a complete neurological recovery. The parents of these seven thought that complete recovery had been achieved within a few months of the onset of illness. One of the two children who had not made a complete neurological recovery (case 10) had minimal weakness of the hip extensors and the ankle dorsiflexors and plantar flexors but negligible functional disability. The other child who had not made a complete neurological recovery (case 3) had minimal wasting of the small muscles of the hands, feet, and calf muscles and there was weakness of the quadriceps, hamstrings, calf muscles, and intrinsic muscles of the feet In this boy charting of muscle strength in the lower limbs ranged between 1 and 4 on the Medical Research Council scale. The boy was unable to walk on his heels and had a waddling gait but nevertheless could walk a mile without tiring and ride a bike for several miles (Table 3) There was no sensory deficit or autonomic dysfunction in any of the nine children

Discussion

Study of the acute illness in our patients revealed some interesting facts. Seven of the 11 children had evidence of pulmonary collapse or consolidation on chest radiograph at the time of admission, indicating that the dangers of oral feeding in the presence of bulbar involvement and poor respiratory function are still not sufficiently appreciated. The degree of

Table 2 *Aspects of ventilation during acute Guillain-Barré syndrome in 11 children. All figures denote days*

	Case No										
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
Initial chest radiograph	A	A	A	N	A	A	N	N	A	N	A
Onset of ventilation	6	7	4	5	6	40	4	10	12	210	180
Duration of ventilation	3	42	56	11	18	21	3	10	21	34	20
Onset of improvement	9	22	24	8	10	54	5	15	—	240	198
Plateau time	3	15	20	3	4	14	1	5	—	30	18

A=Abnormal, N=normal

Table 3 *Clinical features in the two survivors with neurological impairment*

	Muscle wasting	*Weakness*	*Deep tendon reflexes*	*Functional disturbance*
Case 3	Small muscles, hands distal muscles of lower limbs	Interossei distal muscles of lower limbs	Absent supinator, knee, ankle	Heel walking
Case 10	None	Hip extensors, ankle flexors ankle extensors	Absent ankle	Heel walking

radiological abnormality was not gross in any child (the most severe being lobar collapse or consolidation) and not sufficient to account for respiratory failure per se. Weakness of the respiratory musculature led to hypoventilation and atelectasis, and this was aggravated in many cases by aspiration or overspill due to bulbar failure. Although details have not been provided in the adult studies, we believe that for patients of any age with Guillain-Barré syndrome, developing respiratory failure is often worsened by an episode of aspiration and may indeed precipitate the need for mechanical ventilation

All the children had bulbar impairment, but in six there was additional cranial nerve involvement, most often unilateral or bilateral facial weakness. Five developed an encephalopathy, and although this has previously been reported, it is not a commonly recognised feature of the disease [12] Autonomic neuropathy was prevalent, with hypertension, hypotension, and sphincter disturbance among the commonest symptoms Cardiac dysrhythmias are the most hazardous form of autonomic dysfunction. These may occur spontaneously but more often are provoked by some manipulation, such as changing a tracheostomy tube or induction of anaesthesia.[13] [14] Six cardiac arrests occurred in the group (two in one child), and we think that there should be greater awareness of this common complication of the illness.

There were two children in our group with the rare chronic form of the disease (cases 10 and 11). This pursues a slowly progressive or relapsing course and its exact relation to acute demyelinating neuropathy is uncertain [15] [16] Pathological findings in the two illnesses are identical; it is the tempo of clinical evolution that is strikingly different The peak of disability is usually reached slowly in the chronic form (after six to 12 months), with a plateau of disability that may last for many months. Recovery from second and later relapses is usually slow and incomplete

There were two deaths. One girl had the syndrome with a concurrent endocarditis as a result of overwhelming coxsackie B infection. She developed intractable heart failure and postmortem findings confirmed the presence of an endocarditis and demyelination in the dorsal roots of the spinal cord. The second girl (case 11) had the chronic relapsing form of the disease and developed irreversible ventricular fibrillation during induction of anaesthesia for intubation.

At follow up of the nine survivors it became clear that there was little evidence of persisting functional impairment. All the children assessed had impeccable respiratory function (apart from one child with mild asthma) and none had recurrent chest infections. In the two children who had abnormal neurological signs one had minimal functional deficit and the other's ability to lead a normal life was only mildly affected.

In Winer's study on adults outcome was graded according to a simple objective of functional ability at 12 months after illness, as follows:[11]

(0) Healthy.
(1) Minor symptoms or signs.
(2) Able to walk five metres without help, walking frame, or stick but unable to do manual work, including shopping or gardening.
(3) Able to walk five metres with help, walking frame, or stick.
(4) Chair or bed bound.

(5) Requiring assisted ventilation (for at least part of day or night).
(6) Dead.

Patients who were still restricted in their activity (with a functional grade of 2 or greater at this time) were considered to have a poor outcome; a score of 0 or 1 denoted a good outcome. Twenty nine patients in his adult series were ventilated and 16 (55%) scored badly. By contrast, considering our nine children with the classical form of Guillain-Barré syndrome, allowing for the one death in this group, all our eight survivors scored very well (functional grade 0 or 1). Although our highly selected group is small, outcome in our children thus seems at variance with the adult experience. We acknowledge that there are inherent difficulties in making a direct comparison between our group of patients and the adult series, particularly in a retrospective study, but it does seem that children requiring ventilation for Guillain-Barré syndrome do well, and the need for ventilation need not necessarily be considered a bad prognostic factor.

Management of this condition remains controversial. Although five of our children received steroids at some time during their acute illness, several recent large trials in adults have shown such treatment to be of no benefit in this condition.[6 7] There is some anecdotal evidence that chronic demyelinating neuropathy responds to plasmapheresis,[15 17] and in our two patients with this disease we performed plasmapheresis and used immunosuppressants.[18] The patient who survived seemed to respond appreciably to this treatment and has made an almost complete recovery (case 10). A recent American multicentre trial has shown plasmapheresis to be effective in acute Guillain-Barré syndrome in adults, both in reducing duration of the disease and improving neurological outcome.[2] As most adult patients recover spontaneously, however, it has been advocated that the potentially complicated, uncomfortable, and costly treatment of plasmapheresis should only be employed in those patients likely to have a poor outcome—that is, most of those requiring ventilation.[9 10]

The findings in our group suggest that the outcome in severe Guillain-Barré syndrome in childhood is much more favourable than in adults We believe that provided the child survives the acute illness the prognosis for good functional recovery with intensive supportive measures only is excellent.

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Short reports

Forehead plaque: a presenting skin sign in tuberous sclerosis

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SUMMARY The forehead plaque can be the earliest skin manifestation of tuberous sclerosis and its presence may lead to early diagnosis and appropriate genetic counselling.

Plaques, usually found on the forehead, are a feature of tuberous sclerosis. They are smooth patches of slightly raised skin with a reddish or yellowish discoloration and are now regarded by Gomez as pathognomonic of the condition (Gomez MR. Personal communication.) The earliest skin manifestations of tuberous sclerosis are usually hypomelanic macules[1] and, rarely, depigmented hair patches.[2] Hypomelanic macules are present in 90% of patients with tuberous sclerosis but may be late appearing.[3] We present two patients in whom a forehead plaque appeared before any of these more recognised skin signs.

Case reports

Case 1. This boy was born in 1978. He had no family history of tuberous sclerosis. At 3 months of age he presented to his general practitioner with infantile spasms, though these were not initially recognised as such. By 7 months he was referred to a paediatric clinic where an electroencephalogram showed hypsarrythmia. He was begun on treatment with steroids. A large raised lesion of reddish coloration was present on the right side of his forehead, which was initially diagnosed as a haemangioma. It had been first noticed by his parents at 4 months. No other skin signs were present on examination at this time. By 2 years hypomelanic macules had appeared and he had a cranial computed tomogram taken, which showed an area of increased density (not calcified) in the head of the right caudate nucleus with mild ventricular dilatation. Later that year, a retinal phakoma and a cardiac rhabdomyoma were discovered. By 4 years, facial angiofibromas and shagreen patches had appeared (Figure).

Case 2. This girl was born in 1984 She had no family history of tuberous sclerosis She presented with infantile spasms at 5 months and a computed tomogram taken at that time showed periventricular calcification consistent with a diagnosis of tuberous sclerosis She had no skin manifestations, and a Wood's light examination yielded negative results. At 9 months two small papules appeared on her

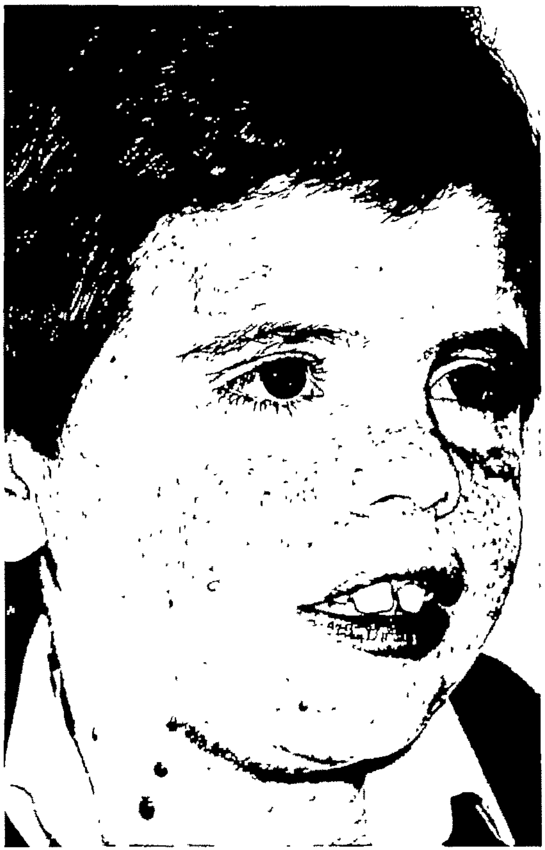

Figure *Case 1 at 8 years of age, showing forehead plaque and facial angiofibromas* forehead, and over the next six months these grew and coalesced into a small reddish coloured plaque. This lesion has subsequently remained the same size. At 2 years two small hypomelanic macules were visible under Wood's light, but no other skin signs have appeared.

Discussion

Seizures in the first year of life, especially infantile spasms, are an important presenting feature of tuberous sclerosis. Early diagnosis is important for genetic counselling and predicting prognosis. In infants with infantile spasms a careful search for the signs of tuberous sclerosis should be performed, in particular, skin examination (including Wood's light), retinal examination, and cranial computed tomography. Diagnostic skin signs (facial angiofibromas, ungual fibromas, and shagreen patches) are rarely present at this age, and a family history of tuberous sclerosis is only occasionally obtained. Much emphasis has thus been placed on finding depigmented patches of skin or hair. These lesions occur in 90% of cases eventually but are present in only 60% at presentation with tuberous sclerosis. Furthermore, the presence of a single white patch is difficult to interpret, as an examination of normal newborns' skin has shown that 0·8% have hypopigmented naevi 1–2 cm in diameter, which may subsequently disappear [4]

Attention has only recently been drawn to the diagnostic importance of the forehead plaque. Histologically, these lesions are similar to facial angiofibromas, except that they have a less prominent vascular component.[5] The two cases presented here illustrate the importance of the forehead plaque as an early sign of tuberous sclerosis. Its recognition in case 1 would have led to the diagnosis being made at the time of presentation. In his case other signs appeared much later and even his computed tomogram in isolation was not diagnostic, having only a single non-calcified paraventricular lesion. The plaque was initially misdiagnosed as a strawberry naevus, which should appear shortly after birth. In case 2 the plaque remains the clearest sign. though the diagnosis was established early by computed tomography.

We thank Dr D C L Savage for permission to report one of his patients

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Mercury as a health hazard

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SUMMARY Pink disease has virtually disappeared since teething powders were withdrawn.[1] We describe a case in a boy who was exposed to metallic mercury vapour. We discuss the potential health hazard of spilled elemental mercury in the house and the difficulties of removing it from the environment

Case report

The patient was the only child of healthy unrelated parents There were no perinatal problems and his early developmental milestones were normal His general health was good until the family moved house when he was 18 months old. One month later he became irritable and anorexic. He developed a cough and began dribbling saliva. His hands and feet became swollen. He could no longer walk and had difficulty sitting upright. Over the next few months he gradually lost his language and social skills and became apathetic and withdrawn.

On examination his hands and feet were swollen, with bright pink peeling skin. He was sweating excessively yet was apyrexial. The optic fundi were normal, as were his cranial nerves. There was pronounced proximal muscle weakness and hypotonia of both upper and lower limbs. He was unable to sit unsupported. The peripheral muscle strength was normal. All tendon reflexes were present but reduced. His blood pressure was normal at 80/50 and the remainder of the systemic examination was unremarkable.

The clinical diagnosis of pink disease was supported by a urinary mercury concentration of 350 nmol/l (normal <100 nmol/l). Neither his father nor his mother were symptomatic, their urinary concentrations being 26 and 72 nmol/l, respectively.

A detailed history of treatment with drugs excluded the possible ingestion of any mercury containing compound, but the parents learned that the previous occupants of the house had used mercury either to silver telescopic mirrors or to guild replica coinage. This family had left the area and their state of health was not known.

A search of the child's home for environmental mercury was conducted with a Data Acquisition DA 1500 portable mains operated mercury vapour detector. This instrument has a threshold of detection of roughly 1 μg/m^3 of air. Airborne concentrations downstairs were low (<3 μg/m^3) and no source could be found Upstairs appreciable concentrations were found in the baby's bedroom (10–12 μg/m^3), with much higher concentrations near the vacuum cleaner and near floor level (up to 300 μg/m^3). Lifting the loosely laid carpet revealed droplets of mercury on the linoleum underneath, and the carpet back was impregnated.

Recommendations were given concerning decontamination procedure. The local authority engaged a firm of house preservation specialists who dusted the floor with flowers of sulphur and unsuccessfully attempted to remove the sulphur and mercury with the household vacuum cleaner. This procedure was repeated using an industrial vacuum cleaner that was neither fitted with high efficiency exhaust filtration nor vented outside the house. These actions disseminated mercury throughout the house (up to 1000 μg/m^3)

Instruction was then given to the firm to use washes of slaked lime and flowers of sulphur rather than dry sulphur and to use detergent to recover the now widely distributed sulphur dust, as it was shown by lifting the floorboards that the mercury had penetrated to the joists and supporting brick work. After the adoption of satisfactory and thorough procedures mercury concentrations did not exceed 1 μg/m^3 throughout the house and the family reoccupied it.

After admission to hospital the baby showed signs of slight improvement and in view of this penicillimine, a potentially toxic drug, was not prescribed. Over the next three months the child made a gradual but complete recovery. The last sign to disappear was the hypotonia.

Discussion

Metallic mercury is volatile at room temperature Concentrations of vapour up to 3000 μg/m^3 can arise from spilled elemental mercury at room temperature, depending on the conditions of ventilation. The current standard for occupational (inhalation) exposure to mercury vapour is given by the Health and Safety Executive as a recommended occupational exposure limit of 50 μg/m^3 (eight hours time weighted average value) applicable to long term exposure.[2] This is a standard for adults at work and must not be used as a 'safe concentration' for domestic exposure nor for children.

The developing infant was exposed to a higher concentration of mercury while crawling on the floor (300 μg/m^3) than occurred in the room environment at a height of 1·5 metres (10–12 μg/m^3). An infant is also liable to retain higher percentages of absorbed mercury in the brain than an adult. A number of cases of excessive absorption of mercury have been reported ensuing from the introduction of metallic mercury in an uncontrolled manner in the home.[3–6] We suggest mercury may be found where:

(1) The premises were formerly used by a business, such as dental surgery, laboratory, instrument or jewellery manufacture or repair, farming, or police.

(2) Domestic equipment—for example, a barometer—has been broken or children or hobbyists have used mercury.

This case shows the importance of spilled elemental mercury as a potential health hazard in the home and underlines the need for specialist professional guidance for organisations undertaking the removal. The authors (RLK, AHS) will be pleased to give advice and the British Occupational Hygiene Society (1 St Andrews Place, Regents Park, London NW1 4LB) will refer an enquirer to an appropriate regional authority.

We thank Professor O P Gray for his help and allowing us to report his patient

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Transient congenital hypothyroidism after topical iodine in pregnancy and lactation

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SUMMARY A 6 week old girl with transient congenital hypothyroidism is described. The hypothyroidism was associated with multiple applications of povidone iodine during pregnancy and lactation This case illustrates the potential hazard of using topical solutions containing iodine during pregnancy and lactation.

Congenital goiter and, rarely, transient hypothyroidism have been reported to occur sporadically in infants whose mothers received iodides during pregnancy for a variety of non-thyroid diseases or hyperthyroidism.

In these cases iodides had generally been taken orally by the pregnant mother.[1, 2] A few cases of congenital transient hypothyroidism secondary to maternal exposure to procedures using contrast media that contain iodine have been described.[3]

We report a case of a prolonged but transient hypothyroidism without goiter in a girl whose mother used povidone iodine preparations during pregnancy and lactation.

Case report

A 6 week old Jewish girl of Ashkenazi origin, the youngest of five healthy siblings, was referred to our day care unit because of a low serum total thyroxine concentration of 3 μg/dl (normal value >7 μg/dl) revealed by routine screening for congenital hypothyroidism. She was born at term after an uneventful pregnancy and delivery. Her birth weight was 4000 g. During the pregnancy the mother washed herself almost daily with a solution of povidone iodine, which is a complex of iodine and polyvinylpyrrolidone, which releases free iodine in solution, with 1% available iodine. She had also rubbed large areas of her skin with povidone iodine ointment (1%) because of spreading furunculosis. These procedures were continued during lactation until referral.

The mother's aunt and uncle suffered from a thyroid disorder, the nature of which could not be elucidated.

Physical examination revealed an infant in good condition with mild jaundice. Her weight was 5·1 kg, length 54·5 cm, and head circumference 40 cm. Body temperature was normal. No goiter was palpable. The face was round with a protruding tongue. Respiration was noisy but there were no signs of respiratory distress The abdomen was large and the liver was palpated 3 cm below the costal margin. A large umbilical hernia was present. Neurological examination yielded normal results, except for moderately delayed deep tendon reflexes. Laboratory tests revealed a serum concentration of free thyroxine 0·4 ng/dl (normal values 0·7–2 ng/dl). Thyroid stimulating hormone (TSH) was 99 μU/ml (normal value 0·8–5 μU/ml). Indirect bilirubin was 5·6 mg% (95 μmol/l). Thyroid antibodies were negative in the child and her mother. A thyroid scan yielded normal results.

A diagnosis of primary hypothyroidism was made on the basis of raised TSH and decreased thyroxine concentrations. Treatment with L-thyroxine sodium was started. On follow up, there was an increase in thyroxine and a decrease in TSH concentrations (Table).

Table *Clinical, laboratory, and pertinent therapeutic data in a case of transient congenital hypothyroidism associated with maternal application of povidone iodine during pregnancy and lactation*

Age (months)	*Weight (kg)*	*Length (cm)*	*Free thyroxine (ng/dl)*	*Thyroid stimulating hormone (μU/ml)*	*Treatment with L-thyroxine sodium (μg)*
1.5	5.1	54.5	0.4	99	50/day
2	5.5	56.5	3.5	5.7	50/day
2.75	6.0	59.6	3.4	1.5	25/every two days
5	7.0	62	2.1	1.5	25/every two days
7	8.0	66.5	1.6	3.3	25/every two days
8*	—	—	1.8	2.7	—
12	10.8	74		Discharge	

*Bone age 6 months (according to Greulich and Pyle)

Growth and psychomotor development were normal. Treatment was stopped at the age of 7 months. At 1 year growth and development were normal.

Pertinent clinical and laboratory data are summarised in the Table.

Discussion

Iodide inhibits biosynthesis and secretion of thyroid hormones if a certain threshold is reached in the serum.[1] Iodide readily crosses the placenta.[3] Transient congenital hypothyroidism with or, rarely, without goiter has been reported to occur sporadically in infants whose mothers ingested iodides during pregnancy for asthma or hyperthyroidism.[1,2] Other cases have occurred after various procedures, such as intravenous pyelography, amniofetography,[3] or topical application of iodine solution during labour or delivery.[4,5]

To our knowledge no case of transient congenital hypothyroidism due to topical application of iodine by the pregnant mother has been reported. Our case illustrates the potential hazard of topical iodine during pregnancy. The use of iodides should also be prohibited during lactation because the iodide is readily secreted into the milk.[1]

Impairment of thyroid function due to iodides is transient. After withdrawal thyroid function returns to normal within two to six weeks.[1] In cases of congenital hypothyroidism replacement therapy should be started to avoid brain damage, even if it is thought that the hormonal impairment might be transient.

In this instance the mother stopped iodide applications, and we encouraged the continuation of breast feeding and began treatment with L-thyroxine. This treatment should be carefully monitored by clinical and laboratory tests. In previously reported cases of transient congenital hypothyroidism replacement therapy has been stopped after a few months, even though thyroid function returns to normal much earlier. As povidone iodine is a common topical antiseptic, not always considered by the mother as a drug, this may explain the aetiology of cases of transient congenital hypothroidism with high serum and urine concentrations of iodine that have been reported.[6] Topical iodine products should be avoided during pregnancy and lactation.

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Neural tube defects in rural Ireland

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SUMMARY The incidence of neural tube defects in a rural area of the west of Ireland from 1974 to 1985 was 2·96 per 1000. The prevalence was unchanged during the 11 years. When compared with a control group there was no increased incidence of anaemia in mothers of affected infants.

The incidence of neural tube defects in Ireland, as in most countries, is falling. Four Dublin maternity hospitals reported an incidence of 6·6 per 1000 from 1970 to 1973[1] compared with an incidence of 3·98 per 1000 from the same area 10 years later.[2] This fall in incidence has not been influenced by induced abortions as pregnancy termination is not carried out in Dublin. A similar fall in incidence has occurred in other countries.[3]

The incidence of neural tube defect is higher in Ireland than most other countries, even allowing for the impact of antenatal screening and pregnancy termination. In Strasbourg from 1979 to 1983 the rate, including induced abortions, was 1·02 per 1000 compared with a rate in Dublin over the same period of 3·98 per 1000.[2]

It is unknown whether the incidence of neural tube defects is similar in all areas of Ireland and whether the prevalence is falling in all areas. This survey aimed to report the incidence of neural tube defects in an area of rural Ireland from 1974 to 1985 inclusive, to see if there was a change in the prevalence; and to determine if anaemia was more common at the first antenatal visit in mothers who subsequently delivered an infant with a neural tube defect.

Patients and methods

Portiuncula Hospital serves a mainly rural population in the west of Ireland. This retrospective study was based on records of all infants over 28 weeks' gestation delivered in the hospital during the years 1974 to 1985 inclusive. All available data, including maternity annual reports, maternity charts, delivery registers, and baby unit records, were examined to identify those infants born with neural tube defects. Cases of neural tube defects were defined as infants with anencephaly, spina bifida aperta, or encephalocoele.

Results

During the 11 years there were 22 272 infants born with a gestational age of over 28 weeks. A neural tube defect occurred in 66 infants—an incidence of 2·96 per 1000 births. The yearly incidence of neural tube defects (Table) was analysed using the Wilcoxon rank sum test, taking into account four tied ranks. This showed no significant change in incidence over the 11 years ($\lambda=0\cdot003$)

Of the 66 infants, 32 (49%) had spina bifida, 28 (42%) had anencephaly, and six (9%) had an encephalocoele.

The overall perinatal mortality was 67%. Of the 38 infants with spina bifida or an encephalocoele, 16 (42%) were perinatal deaths, six (16%) were late deaths, and 16 (42%) are still alive. Nine of the survivors are normal or have mild handicap and seven have moderate or severe handicap.

We compared haemoglobin concentrations at the first antenatal visit in mothers of infants with neural tube defects with the next 66 mothers of similar age, parity, and social class who delivered a normal infant. Neither group of patients was receiving periconceptual vitamin or iron supplements.

Eleven of the group with neural tube defects had haemoglobin concentration of less than 11 g/dl compared with only three of the control group. The

Table *Yearly number and incidence per 1000 of cases of neural tube defects*

	Year										
	1975	*1976*	*1977*	*1978*	*1979*	*1980*	*1981*	*1982*	*1983*	*1984*	*1985*
Deliveries	1349	1518	1608	1588	1776	2126	2302	2444	2364	2482	2428
No with neural tube defects	7	4	5	4	1	10	3	4	4	13	11
Incidence (per 1000)	5·2	2·6	3·1	2·5	0·6	4·7	1·3	1·6	1·7	5·2	4·5

mean (SD) haemoglobin of 11·6 (3·3) g/dl in the group with neural tube defects compared with 11·8 (2·7) g/dl in the control group and was not significantly different (t=0·38, p=0·7)

Discussion

There is a significantly higher incidence of neural tube defect in the main population centres on the east coast of Ireland. The incidence in Dublin is 3·98 per 1000 and in Belfast is 3·86 per 1000,[2] and both are higher than our own incidence of 2·96 per 1000 It may be that our lower rate reflects differences in nutritional state and social structure. Unlike reports from other areas, we have not noted a change in the incidence of neural tube defect over the 11 years.

A possible link between nutritional factors, particularly folate deficiency, and neural tube defect was first reported in 1965 [4] Smithells *et al* suggested periconceptual multivitamin supplementation as a method of reducing the incidence of neural tube defects.[5] In our study there were no significant differences in haemoglobin values at the first antenatal visit between mothers of children with neural tube defects and a control mothers. We have no data, however, for folate or vitamin B_{12} concentrations.

We thank Vida Tansey for statistical help

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Anti-rotavirus antibody in cerebrospinal fluid

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SUMMARY Ten infants with benign convulsions associated with rotavirus gastroenteritis had no specific antibodies in cerebrospinal fluid by enzyme linked immunosorbent assay (ELISA). On the other hand, eight of 173 patients with other neurological diseases had specific IgG, IgA, or IgM antibodies. The reason for positive ELISA results is discussed.

We have reported a case of suspected rotavirus encephalitis detecting anti-rotavirus antibody in cerebrospinal fluid (CSF) by enzyme linked immunosorbent assay (ELISA) in this journal.[1] We further examined anti-rotavirus antibody in CSF specimens from other cases with neurological involvement to discover the relation between rotavirus and diseases of the central nervous system.

Patients and methods

Fourteen CSF specimens from 10 infants with benign convulsions associated with rotavirus gastroenteritis and 230 CSF specimens from 173 patients with other neurological diseases were examined for anti-rotavirus antibody. The specimens were centrifuged and supernatant stored at −20°C until tested.

ELISA for antibody measurement was assayed using purified human rotavirus (serotype 4, subgroup II) and affinity purified peroxidase labelled goat antihuman IgG, IgA, and IgM antibodies.[1,2]

Antirotavirus antibody in CSF was considered to be positive when the optic density of an examined 10-fold diluted CSF specimen was more than that of 1000-fold diluted positive control serum, because (1) if serum anti-rotavirus antibody penetrated passively to CSF the value in CSF was less than 100-fold that in serum, and (2) the mean optic density plus two standard deviations of negative samples was almost the same optic density of the 1000-fold diluted positive control serum. Positive samples were examined in duplicate and in a blocking assay.

Results

Fourteen CSF specimens, four paired and six at acute phase, from 10 infants with benign convulsions associated with rotavirus gastroenteritis yielded negative results. Eight (17 CSF specimens) of 173 patients (230 CSF specimens) with other neurological diseases yielded positive results. These positive specimens were pretreated with rotavirus and showed more than 50% blocking.

Twelve specimens were positive in specific IgG, eight in specific IgM, and seven in specific IgA. The positive cases comprised one newborn infant with *Escherichia coli* meningitis simultaneously afflicted with rotavirus gastroenteritis, one infant with group B streptococcus meningitis who later had rotavirus gastroenteritis, one child with mumps meningitis, one child with Japanese encephalitis, three adults with brain tumour who received chemotherapy and radiation treatment, one adult with neuro-Behcet's syndrome, and one child with congenital brain anomaly and hydrocephalus with shunt treatment.

Discussion

Rotavirus is an important cause of acute gastroenteritis in children. Patients with convulsions, encephalopathy, and (suspected) encephalitis have occasionally had rotavirus gastroenteritis.[1 3 4] Anti-rotavirus antibodies were found in CSF specimens of patients with neurological diseases that might not be caused by rotavirus infection. From these studies it was suspected that the raised anti-rotavirus antibody titre was due not only to invasion of rotavirus into central nervous system (our former case report[1]) but also due to impairment of blood brain barrier or non-specific intrathecal production (our 17 cases and the patients with multiple sclerosis reported by Vartdal *et al*[5]).

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Improving facilities for children in an accident department

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SUMMARY A separate waiting and treatment area for children was established within an existing general accident and emergency department at relatively little cost. We describe how this was achieved and how it has benefited the children attending the department.

Figures for attendances by children at accident and emergency departments in the United Kingdom are incomplete, but it has been estimated that there are two million such attendances annually.[1] In South Glamorgan we have shown that up to 20% of the population under the age of 15 attend the accident and emergency department in a year.[2]

It is generally recognised that children should be given priority with their assessment and should not be expected to wait and be treated in the proximity of ill, and occasionally violent and abusive, adults. The provision of separate waiting and treatment areas is a logical way of dealing with this problem and has been recommended for many years.[3] The Court report, however, showed that only 11% of accident and emergency departments provided separate facilities for children.[4] In a more recent survey by the British Paediatric Association standing committee on accidents in children only 25% of hospitals that replied to a questionnaire provided separate waiting and treatment areas.[1]

We describe how paediatric accident and emergency services were improved in an already existing general accident and emergency department at our hospital, with benefit to the patients and staff and with relatively little expenditure

Methods and results

Our hospital is the only one with a major accident and emergency department in South Glamorgan, where the population in 1984 was 394 400, including 76 800 children under the age of 14. This population increases in the summer months with tourism. In 1985 there were 93 000 attendances, of which 75 000 were new. Mean daily attendances of children 14 years and under varied from 33 in January 1986 (range 19–49) to 61 in June 1986 (range 45–85) The department itself was originally converted from two 'Nightingale' wards built in 1883. One hundred years later, although priority was given to children, they were still managed alongside adult patients, sharing common waiting areas and treatment rooms.

In 1983 the consultants in the accident and emergency department, together with the liaison consultant paediatrician, decided to establish a separate paediatric unit within the department There were initial reservations about this move from some senior nursing and clerical staff and there were also considerable financial constraints.

A rather spacious plaster room was used only in the late evenings and overnight, and a waiting area for this facility was in close proximity. The conversion involved separating this plaster room into two areas by a partition wall, and a much smaller area was retained as the plaster room. This left a small, but none the less adequate room, 9'×14', which already contained suction and oxygen points and a series of wall cupboards, all of which were retained. The area outside was converted into a combined waiting/play area. Toilet facilities were already available and were retained for use by the paediatric unit. Facilities for mothers to feed and change their babies were provided. The total cost of this conversion was under £2000, including provision of the partition wall, decoration, and labour (1983 costs).

Children arrive through a common entrance and reception area and are registered before being directed to the paediatric area. Only children under the age of 11 are managed in the unit because of the restriction of space. The recently converted room is used for assessment, for treatment, and also as a redressing clinic, and a dental suite opposite is readily available and used for some suturing. Facilities for the resuscitation of the very severely ill and injured child are shared with adult patients in a separate area where ensuite *x* ray is available.

The paediatric unit is staffed between 0900 and 2100h by a registered children's nurse together with nursing staff from the accident and emergency department. A senior house officer from the accident and emergency department rotates through the unit and paediatric junior and senior staff are available for consultation and visit the unit often. A consultant paediatrician has a liaison role and is involved in policy making within the unit.

The initial resistance of some staff has been replaced by enthusiasm. There have been clear benefits in the tolerance of children to examination and treatment and both parents and children find the unit more acceptable and less stressful. Separation of the children from the adults has also helped in the management of the adults.

Discussion

'The optimum care of children in hospital requires specially designed accomodation and professional staff trained to meet their needs and the needs of their parents.'[4]

Despite this, many accident and emergency departments are housed in existing parts of old hospitals and accommodation is far from ideal. Indeed, even some new purpose built departments still lack separate paediatric treatment and waiting areas. Children should be shielded from adverse sights and sounds in an otherwise busy, distressing, and often frightening accident and emergency department. In a recent survey, out of 189 hospitals that replied, 66 did not even keep records of the number of children attending their departments and thus they can make no sensible attempt to estimate the demand children place on their services. In addition, only 15% provided a state registered children's nurse, although 47% had access to a liaison health visitor. There is obviously room for improvement.[5]

There are only two consultants in paediatric accident and emergency medicine in the UK (Liverpool and Sheffield) and most children attend a general accident and emergency department, under the supervision of an accident and emergency consultant, where children account for between a quarter and a third of total attendances.

The causes of attendance vary from trauma, acute illness, child abuse, and social disease to cot deaths, and staff should be adequately trained to deal with these matters and provided with adequate facilities in a warm, well lit area. Indeed, accidents are the principle cause of death between 1 and 15 years of age, and this has major implications for accident and emergency services

Adaptations can be made to improve the delivery of a paediatric accident and emergency service within existing building and financial constraints.

The establishment of the paediatric unit at our hospital has been a success, despite its limitations. The unit is used daily, including weekends, from 0900 to 2100h, when most children attend an accident and emergency department, but it remains impractical to staff overnight with existing restrictions on medical and nursing staff levels. Resuscitation areas are shared, but this would seem to be perfectly acceptable in view of the severity of the illness/accident, the small percentage of children requiring resuscitation, and the high cost of installing such specialised equipment. None the less, some paediatric resuscitation equipment is kept within the paediatric area.

Despite these limitations, however, separate waiting and treatment areas could be established in many existing accident and emergency departments with a little thought and planning and within existing financial constraints.

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Herpes oesophagitis in a healthy 8 year old

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SUMMARY An 8 year old, immunocompetent child developed a severe acute herpetic oesophagitis in the absence of oropharyngeal lesions Intravenous treatment with the antiviral drug, acyclovir, relieved symptoms within 24 hours.

Herpes virus type 1 is a commonly reported cause of oesophagitis in autopsy studies and in immunocompromised or debilitated patients. It has also been reported in otherwise well young adults, causing a self limiting but often prolonged illness.[1–4] The condition seems to be uncommon in healthy children, with only three case reports, all from America, aged under 16 years.[5 6] We report an 8 year old boy in whom the diagnosis would not have been made without the use of upper gastrointestinal endoscopy.

Case report

The patient presented with a three day history of progressive retrosternal pain, made worse by swallowing and unrelieved by aluminium hydroxide. He had been unable to eat solids and had taken only small amounts of fluid. He denied any ingestion of corrosive agents and had previously enjoyed excellent health. His mother and 6 year old brother had a history of recurrent herpes labialis. On examination, he had mild cervical lymphadenopathy and a temperature of 37·7°C. No other abnormality was found, and, in particular, there were no skin or oropharyngeal lesions.

Initial investigations included a normal full blood count and barium swallow examination. The following morning, upper gastrointestinal endoscopy revealed severe inflammation of the whole length of the oesophagus, which was worse distally, with oedema, contact bleeding, and multiple small superficial ulcers (some in clusters, some linear, and some isolated). There was also a copious white, mucopurulent exudate. Biopsy specimens were taken for histopathological and virological examination, and later the same day herpes virus was identified by an electron microscopic immunofluorescence technique. This was subsequently confirmed as *Herpesvirus hominis* type 1 on culture. The virus was not identified from nasopharyngeal secretions. Histology confirmed the acute severe oesophagitis, although Cowdry type B inclusions were not seen.

The patient was begun on intravenous acyclovir 5 mg/kg every eight hours, which was continued for five days. His response was dramatic; within 18 hours he was virtually asymptomatic and able to eat solid food, including toast, without pain. In the six months since discharge he has remained completely well.

A subsequent comprehensive investigation of his immunological system failed to show any abnormality. This included serum immunoglobulins (subclasses), T and B cell numbers, helper/suppressor ratio, in vitro lymphocyte proliferative responses, natural killer cell activity, polymorph function, and complement system. He had antibody titres present to various common viral agents, and his specific herpes antibody titres taken on days 3 and 15 showed a rise from undetectable to 1/20.

Discussion

Labial and oropharyngeal herpes in childhood is common, and some children probably have concomitant oesophageal involvement, although this is seldom sought This case is unusual in that the oesophagus seemed to be the only primary target organ and the oropharynx was completely spared. Upper gastrointestinal endoscopy allowed direct visualisation of the mucosa and the opportunity to obtain tissue for diagnostic purposes. Because of the degree of dysphagia, barium studies may be difficult to perform and as in this case do not always show an abnormality. Although the previous case reports have stated that the children were 'healthy' or 'immunocompetent', this in fact was assumed from their previous histories and comprehensive immunological studies were not performed.[5 6] The duration of symptoms, in both children and young adults, receiving symptomatic treatment only has been reported as three to 17 days.[1–6] Our patient responded to acyclovir in less than 24 hours

Herpes oesophagitis seems to be an acute, often prolonged, but self limiting condition. We suggest that it should be added to the differential diagnosis of acute oesophagitis, that endoscopy and biopsy examination be the investigation of choice, and that specific antiviral treatment may be beneficial.

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Neonatal candida septicaemia: diagnosis on buffy smear

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SUMMARY We report a case of neonatal candida septicaemia diagnosed by examination of a buffy smear. This would seem to be a fairly simple test for a disease where a good prognosis is dependent on rapid diagnosis and isolation using standard culture techniques is notoriously unforthcoming.

Case report

A preterm female baby with a gestation of 25 weeks and a birth weight of 790 g was born by emergency caesarean section and transferred ex utero for intensive care. The baby developed moderate hyaline membrane disease that required ventilation at maximum pressures of 22/4 cm H_2O and a maximum fractional inspiratory oxygen tension of 0·9. Prophylaxis with antibiotics was with penicillin and gentamicin. Intravenous feeding through a central venous catheter was begun on day 15, ventilatory requirements having fallen. Cefuroxime had been substituted for penicillin due to the isolation of a coagulase negative staphylococcus from tracheal aspirate in association with a lobar collapse.

On day 28 the baby, still ventilated, developed a metabolic acidosis and poor peripheral perfusion, and the inspired oxygen requirement rose again. A chest *x* ray film was non-contributory and a full septic screen, including culture of suprapubically aspirated specimens of urine, blood, and cerebrospinal fluid, yielded negative results for bacteria. A scanty growth of candida had been isolated from an umbilical and rectal swab one week previously but not subsequently. Invasive sepsis was suggested by a raised blood immature:total neutrophil ratio (maximum value obtained=0·59, normal=<0·16[1]) and a raised C reactive protein concentration (maximum value obtained=47 mg/l, normal=<5 mg/l). The changes in these values are illustrated in Figure 1. Treatment with antibiotics was changed to vancomycin and chloramphenicol and the central venous catheter was removed. Over the next 48 hours the baby continued to deteriorate with worsening hypoxaemia.

On days 31 and 32 blood samples were taken specifically to exclude a diagnosis of candida septicaemia. The initial sample was taken from an indwelling peripheral arterial cannula and the later sample from a separate sterile arterial puncture. Both samples were handled aseptically and processed in identical ways. Each was separated by centrifugation at 400 *g* for seven minutes and the buffy layer of cells removed with a sterile pipette. The buffy layer was then spotted on to a glass slide cleaned with alcohol and a smear made in the standard manner. A Gram stain was performed and the slides examined under ×100 magnification oil emersion lens. Each smear showed large inclusions within the phagocytic leucocytes, which were stained Gram positive and were oval in shape, characteristic of a yeast. It was possible to see budding of the yeast cells within some of the leucocytes (Fig. 2). The fact that the yeast was seen intracellularly from two separate samples convinced us that this was a true fungaemia rather than contamination from the skin, of the indwelling cannula, or of the slides during preparation.

Blood samples were sent specifically for culture of

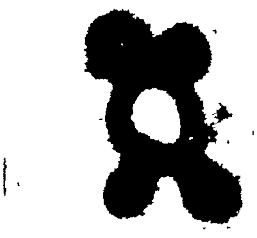

Fig 2 *Leucocytes from a buffy smear visualised on high power light microscopy A yeast cell that has budded in four places within the leucocyte is shown*

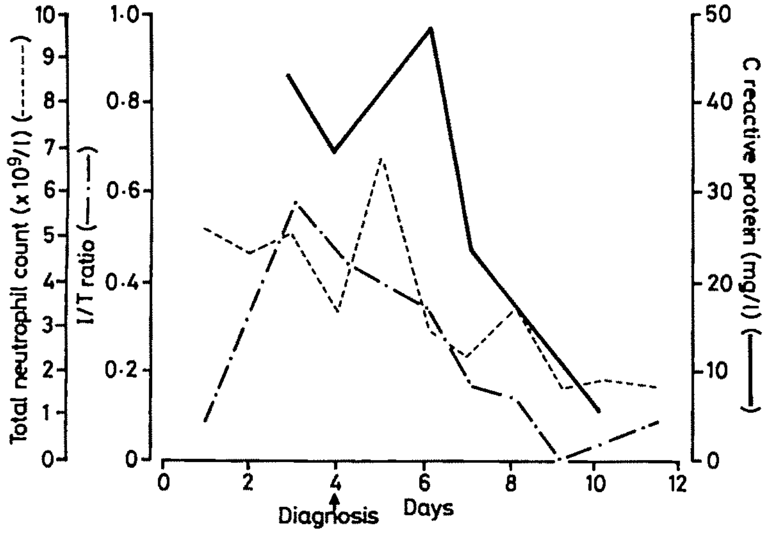

Fig 1 *Total neutrophil counts, immature. total neutrophil (I/T) ratios, and C reactive protein values from 27 days of age through the period of candidal infection. Antifungal treatment was begun on the day of diagnosis*

candida both before and after beginning antifungal treatment. Each blood sample was inoculated into a standard brain-heart infusion broth blood culture system, incubated at 35°, and examined daily.

After visualisation of a yeast on buffy smear the baby was begun on 5-flucytosine and amphotericin at standard neonatal doses, the latter being increased over the first four days. Flucytosine was maintained at therapeutic concentrations (25–80 mg/l). Forty eight hours after the start of antifungal treatment the baby had improved markedly, adding further support to the diagnosis. Candida was only isolated from one blood sample, which had been sent after beginning antifungal treatment, and was identified as *Candida pseudotropicalis.* A repeat buffy smear five days after starting treatment yielded negative results for yeasts and further blood and urine samples also yielded negative results. There was no reoccurence clinically; the baby was extubated on day 60 and discharged well four months later.

Discussion

Systemic candidiasis is a serious problem in newborn infants who, particularly when severely preterm, are immunologically unprimed and depleted. Maternally derived immunoglobulin G, necessary for candidal opsonisation, is present at particularly low concentrations in the very preterm infant and continues to decline until at least 15 weeks after birth.[2] Phagocytosis is usually efficient in the preterm baby (as shown in this case) but intracellular killing is often impaired, particularly in stressed infants.

Candida is a particular threat as it is notoriously difficult to isolate rapidly. Involvement of the renal tract is common and examination of suprapubic urine for budding yeasts important in suspected cases.[3] Such samples are not easy to acquire, however, in the smallest babies and even if positive do not guarantee systemic involvement. The buffy smear technique permits examination of small blood samples quickly and if positive is diagnostic. Smears of the buffy layer of cells in peripheral blood have been used previously to diagnose bacteraemia with conflicting reports.[4 5] The risk of false positive results when diagnosing yeast infections is less, due to their characteristic appearance on microscopy. In one report blood drawn from central venous catheters was positive for candida in three cases involving older children.[6]

Candida septicaemia in this report was diagnosed by an inexperienced observer, illustrating both the simplicity and importance of this test. All cultures yielded negative results before antifungal treatment, and a diagnosis that enabled the start of appropriate treatment was achieved solely using this technique. As recovery from candidiasis seems to rely heavily on early diagnosis and prompt treatment we would strongly advocate that examination of a buffy smear in suspected cases be performed.

We thank the staff of the mycology department, St Mary's Hospital, for their contribution

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Personal practice

Management of obesity

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We all think we understand obesity The layman can recognise it as readily as the specialist as severe cases are obvious, but distinction of the normally fat from the mildly obese is extremely difficult. Superficially, the explanation for obesity is also simple. Obesity results from an excess of energy intake over energy output. Consequently, reducing energy intake leads to fat reduction and cure. Ergo, the obese are either greedy or lacking in willpower—neither creditable traits.

These views are, of course, too simplistic. Overwhelming evidence that the obese eat more than the non-obese is lacking [1-3] Dietary restriction is notoriously ineffective. Yet perhaps this too is a misrepresentation Children may slim spontaneously during late infancy, male adolescence, and at other ages.[4-6] Obesity is widely understood to be cured by dieting Both adults and children may restrict their intakes when they notice obesity and lose weight successfully without medical advice Success with slimming regimens has been described as inversely related to the degree of medical involvement[7] but, given the above, this could be expected. The obese referred for help are those who have greatest predisposition to obesity or greatest resistance to slimming, or both.

What are we trying to achieve by treating obese children?

Ideally, the aims of treatment of obesity would be to achieve appropriate weight for height and age and to keep weight within the normal range, while allowing normal growth. This is possible for moderately obese young children with much growth ahead. It is probably not possible for many grossly obese adolescents, particularly severely obese girls who are postmenarche. Yet if cure is not possible any reduction in fat will still improve appearances, increase mobility, increase opportunities for buying attractive clothes, and, possibly, diminish morbidity from the hazards of obesity that occur in adult life I treat obesity on the assumption that some loss of fat is worth achieving, even if appropriate weight for height and age is not attained

Where should obese children be treated?

Obesity clinics have many advantages (Table 1) but will not be available to all Hospital management is not essential After initial assessment obese children can probably be managed as well by any interested and knowledgeable person as by a paediatrician. Clinics held in schools may be more appropriately sited. Whoever looks after these children must understand normal childhood growth and nutrition as well as have a sincere interest in the management of obesity. Group treatment sessions may suit some organisers and some children, but long term results do not suggest that novel approaches to obesity have advantages over more traditional clinics.[8]

Assessment

The first attendance is very important Children with pathological cause for their obesity (Table 2) must be recognised and investigated. Eating habits and the dietary likes and dislikes of the children must be determined. Details of social and family history provide insight into the environmental problems likely to affect children's ability to diet. Baseline anthropometry is obtained and dietary and general guidance provided. Inadequate assessment

Table 1 *Advantages of specialised clinics in treatment of obesity*

Time can be allotted for dietary and behavioural discussion
Concentration of patients makes dietitian's attendance worth while
Precise anthropometry by same observer
Large adolescents less 'out of place' than in general paediatric clinic
Mutual support for families through attendance at one problem clinic

Table 2 *Pathological conditions predisposing to obesity*

Sign	*Cause*
Endocrine	Hypothyroidism
	Growth hormone deficiency
	Cushing's syndrome
	Craniopharyngioma
'Hypothalamic'	Prader-Willi syndrome
	Laurence-Moon-Biedl syndrome
	Carpenter's syndrome
	Alstrom's syndrome
	Pseudohypoparathyroidism
Chromosomal	Down's syndrome
	Klinefelter's syndrome
Drug treatment	Corticosteroids
	Sodium valproate
Reduced activity	Spina bifida
	Duchenne muscular dystrophy
Non-specific causes of mental retardation	
Skeletal causes of short stature	

or indefinite advice given on the first occasion children are seen may be difficult to overcome or correct later.

Table 3 lists particular points of importance in history and examination Children with 'simple' obesity are often from single parent or single child and lower social class families. Eighty per cent will have at least one obese parent.[6] A detailed dietary history is essential, although tedious to obtain. I usually ask parents and children to work backwards over 24 hours recalling the foods eaten and then ask specifically about intake of 'inbetween' foods (sweets, chocolate, crisps and similar packet items, ice cream, biscuits, cake, chips, and 'pop') and the usual intake of bread, potatoes, and milk. Whether weekend diets differ greatly also needs to be determined. Some families can give clear dietary histories. Others insist their child eats nothing. 'Nothing' is sometimes remarkably nutritious!

Children with suspected 'pathological' obesity form a very small proportion of the total population of obese children. Most of them have Prader-Willi or Laurence-Moon-Biedl syndromes or other obvious handicap. Children with pathological obesity usually present with short stature or other symptoms before obesity becomes a major problem. Nevertheless, children whose heights are below the 25th centile for age (obese children are commonly above average stature) deserve at least thyroid function tests, and all deserve more extensive investigation if other features suggest pathological obesity. Occasionally some investigation is necessary to reassure parents that their child does not have a 'glandular' problem and that they must pursue dieting to treat the obesity. The enthusiasm with which children pursue slimming advice is rapidly diminished by suggestions that their obesity may not relate to their food intake Thus I try to remove concerns about disease as quickly and as definitely as possible and then proceed to advise on management.

Table 3 *Particular clinical points of importance in assessment of obesity*

	Clinical point
History	Birth weight
	Age at onset of obesity
	Family history of obesity
	Parental heights and weights
	Family size and structure
	Detailed dietary history
Examination	Distribution of fat
	Presence of hirsutes, striae, or Cushingoid facies
	Orthopaedic problems, especially slipped upper femoral epiphysis
	Blood pressure
	Visual fields
	Pubertal development
	Presence of glycosuria

Clinical examination must include an assessment of pubertal development as this will indicate the likely extent of future growth and present nutritional requirements for growth. During the pubertal growth spurt boys may have enormous intakes[1, 9] and lose fat readily, even on energy rich diets. Postmenarcheal girls have fairly low energy requirements and, as growth has more or less ceased, must concentrate on weight loss if they are to slim.

One of the major health risks to the obese is the second rate medical care they are liable to receive. It is easy to feel impatient or contemptuous with the grossly obese and to attribute their complaints to their size. Hence the need for a sympathetic clinic atmosphere. There is also the sheer impossibility of giving these children the same precise clinical examination given to normal children. Palpation of abdominal viscera through a carpet of subcutaneous and intraperitoneal fat may be impossible. Blood pressure is difficult to measure accurately due to the large arm circumference. I usually use a leg cuff in adolescents, folding it over so it is two thirds the length of the upper arm. The inflatable part of the cuff then encircles the arm, which is necessary for accurate sphygmomanometry.

Anthropometry must be performed carefully and preferably by the same observer on each occasion. Children are weighed in light underwear only. Weights and heights are recorded at each attendance. Beam balance and Stadiometer are advisable. Skinfold calipers are useful but not essential and should not be given too much importance. Very fat children may have skinfolds that are too thick for the gape of the calipers. Before slimming, many have skinfolds that cannot be raised or that will not pull into proper folds so the calipers gradually slip and steady readings cannot be obtained. Once some

Table 4 *Sites for measurement of skinfolds (left side of body) in obesity*

Name of site	*Site*
Triceps	Over triceps muscle midway between olecranon and tip of acromion with arm hanging by the side of the body
Biceps	Over the midpoint of the biceps at same level as triceps fold with arm resting supinated on thigh
Subscapular	Just below the tip of the inferior angle of the scapula at 45° to the vertical
Suprailiac	In the mid-axillary line just above the iliac crest

weight is lost, the folds are raised more easily and a big decrease in thickness recorded, giving a false impression of excessive loss of fat. Skinfolds can be compared with expected values on centile charts[10] but are usually well above normal values in children referred with obesity. Skinfolds can also be used to determine total body fat from regression formulas, but these formulas[11 12] are very imprecise. It is simpler to compare relative fatness by using log conversions of summed skinfold measurements and comparing this data. I measure triceps, biceps, and subscapular and suprailiac folds (Table 4).

Studies of obesity often use weight for height measures as indicators of obesity These have many problems and must be regarded as only approximating to the degree of fatness. The formula chosen should be free of appreciable height bias[13 14] In adults Quetelet's index (weight/height^2=body mass index) is commonly used. In childhood the index has limited use as it varies with age. Body mass index can be related, however, to the index of a theoretical child of the same age with weight and height on the 50th centiles of growth standards to give a % body mass index.[13] This is useful when comparing relative weight of children of different ages or one child on different occasions. Values are usually interpreted as <90%=underweight; 90–110%=normal weight; >110–120%=overweight; >120%='obese'.

Management

Successful management of obesity depends on motivation, decreasing energy intake, and increasing energy output.

Motivation. Motivation is achieved through education, advice, and support. Children and their families need an explanation of obesity other than the interpretation that they must be greedy or feeble because they are obese and cannot slim. I usually suggest that obesity occurs because obese individuals eat more than they need, although this may not necessarily be more than that eaten by their slim friends next door. To slim they need to eat considerably less than at present Exercise, while helpful, is unlikely alone to be sufficient to slim children who are more than slightly overweight.

Parents and children also need to understand the nature of slimming in childhood Almost without exception, slimming in adult life involves loss of excess weight. In rapidly growing children slimming may take place even with slight weight gain. Weight loss adds a bonus of weight not gained as well as weight loss. Indeed, it is sometimes recommended that children should not be encouraged to lose weight when slimming because of the risks of affecting linear growth and lean body mass. Children should be allowed to 'grow into their height'. This may be reasonable for mildly overweight children, but it is not practical for most children referred for slimming advice. Many of these children are above expected adult weight at the time of referral. Others would have to maintain the same weight for four or five years before achieving appropriate weight for height. Thus in most cases some weight loss is advisable, although families must appreciate that as growth proceeds, weight gain will ultimately occur, although fat loss, and therefore slimming, may continue.

Motivation is also helped by frequent clinic attendances. I aim to review children three weeks after first being seen. Longer periods usually mean that children delay beginning dieting until, or give up their diet before, review.

Reducing energy intake. Dieting is basically disciplined eating. Children who are dieting need to learn to have their mouths empty most of the day.

I do not prescribe particular 'calorie' diets. Children come in many shapes and sizes, and within one age group the range of normal intakes even for the normal weight is enormous. Published data provide only broad outlines of the energy requirements of individuals. Therefore I find out in as much detail as possible what the children eat and then adapt this so that eating is at regular mealtimes and snack periods and total energy intake is greatly reduced. This is achieved largely by eliminating snack foods, which are high in energy, low in satiety, and of poor nutrient quality. Energy intakes between 4·2 and 6·3 MJ/day (1000–1500 kcal/day) are the usual result, although very small children may only eat in the lower ranges anyway and teenage boys at the peak of their growth spurt require more than this if they are to both slim and grow rapidly.

The general principles for prescribing diets are outlined in Table 5. The amount of bread allowed depends largely on previous intake, but I usually advise no more than three rounds, except for boys at

Table 5 *General principles for dietary management of obesity*

Confine eating to mealtimes and recognised snack periods
Cut out low satiety, high energy, snack foods altogether—that is, no sweets, chocolate, crisps and similar packet items, biscuits, nuts, ice cream, or cakes
No sugar free chewing gum—children must learn to keep their mouths empty
Avoid fried foods, chips, and adding fat during cooking or serving
Grill, boil, or steam roast instead
No sugar added to cereals, to drinks, or during cooking
'Low calorie' fruit squash and carbonised drinks only
Regulated bread, potato, and milk intake
Consume whole foods where possible as they are often slower to eat and have greater satiety
Modify school meals (Table 7)

their growth spurt. Teenage girls who are post-menarche may require less, as may preschool children. Bread is a useful food, which is quite satisfying and by itself not tremendously fattening. But we rarely eat bread by itself and the butter, margarine, cheese, or jam that go with it greatly increase the energy intake involved with eating bread. Wholemeal bread is no less energy dense but may be more filling and thus more satisfying. It also provides fibre, which is helpful for occasional children who find restricted diets constipating. Milk is another food that should be encouraged in limited amounts. It is a useful source of calcium. I recommend three quarters to one pint a day and no more. Some obese children drink several pints of milk a day. Potatoes similarly provide a source of both energy and other nutrients. One small helping per day of boiled, mashed (with milk but no butter), or baked (without added butter) will make a meal much more filling. Chips should be avoided. Table 6 outlines a typical result of this dietary approach.

Most diet foods and low energy products should be avoided. Many are expensive. Soft margarines, however, are preferable to butter as they can be spread thinly even when taken straight out of the refrigerator. Margarines are also supplemented with vitamins A and D, unlike butter. 'Low calorie' margarines help further as fats are so energy dense that even small quantities on bread may amount to substantial energy intakes. Low energy breads may be useful, but children are likely to eat two slices of low energy bread (or two crispbreads) for every slice of normal bread allowed. This is not helpful as almost the same amount of butter, margarine, jam, or cheese goes on to one slice of low energy bread as on to one of normal bread. Skimmed milk can be used, but in preschool children vitamin intake and growth must be followed carefully. Sugar free and 'low calorie' fruit squash and 'pop' are essential for many children who are dieting as many refuse to drink water. Sugar free whole fruit juices (usually sold in cartons) are a good source of vitamin C and a small glass at breakfast, for example, is acceptable. These juices should not be used as drink instead of squash, as although free from added sugar, the number of compressed fruits in each carton makes them more energy dense than many sweetened drinks.

Table 6 *Outline of possible diet on suggest regimen (roughly 4·2 MJ (1000 kcal))*

Mealtime	*Intake*
Breakfast	Cereal, milk, no sugar and/or one piece of toast, thin scrape of low energy margarine Tea, coffee, no sugar, or glass of milk
Break	Apple/orange
Dinner	Meat, salad, no potatoes Fresh fruit
Home	Cup of tea, piece of toast, or fruit
Teatime	Meat, vegetables, small portion of boiled potato Fruit or low energy yoghurt Tea, coffee, low energy squash, or glass of milk
Suppertime	Piece of toast and scrape of low energy margarine Tea or glass of milk

Some children have undisciplined eating habits and very restricted tastes, with refusal to eat meat, vegetables, salad, or fruit. Such children are a dietitians's nightmare. It may be impossible to design balanced diets that are both slimming and acceptable to them. Sadly, few of them, although miserable because of their obesity, make any effort to learn to like new foods.

School dinners. Until obese children modify their intake at school dinner they are unlikely to slim successfully. Obese children do not require two full cooked meals (dinner and evening meal) each day. There are therefore several alternatives to school dinners (Table 7). All require liaison between parents and school so that schools help, rather than hinder, children's dieting efforts. Problems arise when children are entitled to free school meals and parents resent so little food being provided. If the solution is for the school dinner to become the main meal the evening meal must be light. Children who have potatoes (*not* chips) at school dinner do not need them in the evening. School puddings should be avoided unless fresh fruit or low energy yoghurt can be provided.

Table 7 *School dinners for obese children*

Meat, no pastry, vegetables, no potato, no chips, and fresh fruit or no pudding

or

Salad, no bread, preferably no salad dressing, no potato, and fresh fruit or no pudding

or

Lunch in a box brought from home with salad (cold meat/cheese/hardboiled egg and lettuce, tomato, cucumber, etc) and fresh fruit
Low energy soup in thermos if insist on hot meal

Children who go home for lunch can be given salad or a light snack. Meals such as spaghetti or beans on unbuttered toast are acceptable if quantities provided are modest.

I have not found appetite suppressants any use whatever in the management of childhood obesity and do not use them. I have no experience of novel surgical approaches either, although occasionally there may be older adolescents for whom these procedures are the only hope for appreciable weight loss.

Increasing energy output. I always recommend obese children to increase their output of energy through activity. Most make little attempt to do this until they have lost some weight and feel more mobile. Simple changes in activity include walking to school rather than taking the bus or car; using stairs rather than lifts, and taking up cycling, swimming, or gymnastics in addition to formal games Jogging is a useful way of keeping weight in control, but grossly obese children are often too self conscious to jog to an effective extent. Success with dieting involves a change in lifestyle, and without increased output of energy in activity children are going to have difficulty maintaining fat loss. Some children change their attitude and demeanour completely with the onset of fat loss and become more positive and extrovert.

In addition to exercise, I encourage children to take up hobbies. The difficulties many children have keeping to a diet are due to feeling 'bored' at home. Boredom becomes hunger and they eat. If their minds are occupied, particularly outside home in the evenings and at weekends, the amount of food consumed may be less.

Follow up

I review children within three weeks of first being seen Stimulus to diet follows the knowledge that the situation will be reviewed in the near future At follow up anthropometry is repeated and detailed dietary history obtained with specific enquiries about the 'forbidden' items I take this dietary history before I have informed the children of weight progress as I find when children do not lose weight they are tempted to confabulate over food intake. If the dietary history is incorrect or incomplete it may be difficult to advise appropriately on further action.

As far as possible I try to be fairly positive so that even when children have not lost fat and not dieted well they are encouraged to continue making efforts Where children have gained weight and yet slimmed due to rapid linear growth it is important to explain this achievement to parents and children. Despair and sense of failure develop rapidly and discourage children from persisting with dieting. Where children are consistently making no effort to slim they are presented with an ultimatum: either they make an effort or they are discharged.

When children seem to be established on their diet I lengthen out attendances. I rarely leave appointments longer than every two months unless normal weight for height has been reached. It would be more effective to see children more often, but the number who can be seen at one clinic is not infinite.

Children who fail to slim

Children who fail to slim are, almost invariably, not keeping to the diet described or are dieting for short periods only. There are often good reasons why children fail to diet successfully, although families may have difficulty acknowledging these reasons. Far too many fairly young children are expected to discipline and control themselves irrespective of what the rest of the family (often equally obese) eat around them. Sometimes mothers make no attempt to modify their methods of cooking to produce less fattening diets. Often parents are not strictly honest in the clinic about what the children are eating and children learn that there is no particular reason to be truthful about their intake. Sometimes children do no cooperate with parental efforts to provide a suitable diet. This may be a minor behavioural disturbance but when it becomes sufficient to upset family equanimity or to cause a real rift between child and parents it is doubtful whether it is worth persisting with the slimming regimen. Under such circumstances it is unlikely that efforts to slim the child will be effective anyway

Some children are embarrassed or miserable because they are overweight. Many of these children develop much more positive approaches to school, activity, and relationships with others when they lose weight. Some have major behavioural problems and their obesity is secondary to these These latter children may benefit from psychiatric help if they and their parents are prepared to accept such help—which is not often. But in management of routine cases of childhood obesity I do not feel psychiatric involvement has particular advantages.

Achievements

The diet I prescribe may seem too rigid and puritanical. Normal active children who follow the general principles, however, will lose weight. Many lose weight satisfactorily, despite some dietary lapses. When this is so absolute adherence to the diet is unnecessary, although guidance should be given over where lapses are occurring so that, should slimming cease, action can be taken to modify the diet. I explain to parents and children before they start dieting that dieting is difficult and initially children will feel hungry—but, provided hunger is not sated, that indicates fat is being metabolised Most children find after a few days of sticking to the diet that their appetite lessens.

Sadly, many children referred are so overweight that even if they lose weight at the rate of 500 g a week (a typical initial rate in an adolescent, which generally slows after the first weeks) they may have to diet for a year to lose all their excess weight. Thus, whereas most children who follow the diet initially do lose weight, few manage to persist sufficiently to lose all excess weight. Attitudes to exercise and food change over time, however, and rebound does not necessarily occur—or at least not immediately. Lapses and rebound are common during school holidays and over Christmas. It may be difficult to get children back onto strict diets once major dietary lapses occur

Strict dieting of obese children can lead to slowing of linear growth.[14] This is difficult to assess in children who are in the pubertal age group and consequently crossing height centiles at different ages. It is not a phenomenon I have observed to a great extent.

It is often stated that dieting in childhood should not be encouraged because of the risks of inducing anorexia nervosa. Almost regrettably, none of my obese patients has shown the slightest tendency towards anorexia nervosa. There is, however, a risk that excessive encouragement of slimming programmes for mildly overweight children may induce slimming obsessions among their normal weight peers. It is these latter children who are at real risk of anorexia nervosa.

Prader-Willi syndrome

Children with this syndrome present a desperate problem for which I have no effective answer. Their low intelligence, often negative behaviour, hyperphagia, and low resting metabolic requirements make dietary management extremely difficult. Energy intakes have to be very low (50% or less than expected for age) to achieve weight loss.[15] Relatives, and even parents, may regard such strict dieting as 'cruel' and fail to cooperate with the regimen. As with other children who are uncooperative over dieting there is little point in pursuing diets that precipitate major behavioural disorders or introduce conflict within the family, particularly when, as with Prader-Willi syndrome, long term achievements are so disappointing.

Conclusion

The treatment of obesity is basically a salvage procedure We are trying to correct a situation that should never have arisen. Prevention is more important than treatment. Somehow we need to prevent obesity before it occurs or, at least, treat it before it gets severe Recommendations on prevention abound, but so far there is little evidence of the long term effectiveness of any of these recommendations Without effective means of prevention or novel means of treatment, the alleviation of obesity by exercise and dieting remains the only effective form of management. And its success is limited.

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Personal view

Learning from our patients

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Paediatricians in training learn not merely from tutors and textbooks but directly from children, too. Learning never stops and as we look at their emotional, conceptual, and spiritual development we may still learn from children lessons to apply to ourselves, our society, and our own priorities.

For good emotional development, committed relationships are vital

In the film 'Getting to know each other' Aiden MacFarlane has illustrated excellently the point that new babies are programmed for relationships, the natural key figures being their parents.[1] An older film, by Robertson, 'A two year old goes to hospital', showed the catastrophic effect on the child of an unaccompanied admission.[2] Emotional and physical pining portrayed the child's reaction to this experience. Chronic as well as acute social deprivation produces emotional and physical stunting. All this is now bread and butter to paediatricians and is also recognised intuitively by good parents, whose priority is to diminish problems for the child in crisis whatever the cost to the family. It is when parents are not prepared to think in these terms that paediatricians worry, although to see them respond to gentle pressure is usually to witness the enhancement of all the inter-relationships concerned.

There is, however, a distinction between standing by a child in need, who would not understand alienation, and pandering to that child's wishes for evermore. From toddlerhood on, parents have to learn a new kind of commitment, that of teaching the child that love can include a firm 'no'. Young parents fear that to oppose their child conveys lack of love, and it can be as much a discipline for them to apply correction as it is for the child to be corrected, yet it is in the balanced practice of loving direction that relationships and behaviour both mature. As poor parenting tends to be an inherited disorder and courts and clinics are filled with the consequences of disturbed family relationships, it is never too soon to try to ensure that a child has warm, personal care on the one hand but fair limits to freedom on the other. Discipline may need to be reinforced by the child's temporary alienation within the family—for example, to the bottom step of the stairs—with apology and forgiveness to follow, restoration being marked by a kiss and a cuddle Adapted for age, this process should go on to build the foundation for adult relationships.

Doctors are not immune from problems with relationships and many a doctor's family must know this all too well. It is possible to work very hard at our jobs but to give no input at all to knowing and nurturing friends and relations. Mutual vitality is therefore sapped, to the deprivation of all concerned.

The design for conceptual growth is from egocentricity to altruism

One reason why toddlers get into such trouble is because they are totally egocentric in thought and have yet to learn to see things from someone else's viewpoint. Unenlightened parents (and unenlightened professionals) make the mistake of thinking that children really think like adults and are just being deliberately perverse when they transgress, yet mystifying rules of acceptable behaviour have to be learned and this takes time (and consistency).

A new baby cannot even think in toddler terms, yet there is a noteworthy 'other centredness' made apparent by the great interest displayed in other people from the start. It is this that forms the basis for the child's responsiveness as relationships are built up. Interest in others, however, does not spell understanding of others and in these terms the child remains egocentric for at least two years. This, combined with the growing sense of power experienced with increasing mobility, produces the negativism of the toddler. By 3 years of age, ability to compare self with others has developed so that the concept of being 'big' (and therefore brave) or 'bigger than' (and therefore more deserving or more belligerent) begins here. Things tend to preoccupy

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First presented at the Christian Medical Fellowship breakfast held during the Annual Meeting of the British Paediatric Association in York, 1986 more than people, although there remains a need to report back (on happenings and acquisitions) to care givers. Matching, categorising, and competing all begin in the preschool child and it is appropriate that they should do so. Judgment is, however, entirely face value and the awareness that things are not always what they seem only begins between the ages of 5 and 7. Even then, deductions often remain faulty with a face value element. Hence the child who had heard someone say that we are made of dust and return to dust informed his mother that someone was coming or going under the spare room bed! The double meaning of 'dust' in this context (as well as other proverbs and parables) would not normally be fully understandable until a child reached 10 years of age It is from 11 to 14 years that children begin to think in the abstract, and whereas one may witness a generous spirit in quite little children, true altruism (based on thought for the needs of others in contrast with looking after oneself) is a mark of early adolescence. The response to the Ethiopian appeal by so many teenagers showed how genuine was their concern for others as well as the less mature reaction of copying a pop star.

The whole design in conceptual growth is, therefore, one of getting away from *self* centredness and enhancing *other* centredness, which was there from the start but needed to grow into full potential. Growth spurts may be painful and children need loving, understanding supporters to ensure that painful experience results in growth rather than arrest. Prolonged illness, with recurrent hospital attendance, will accelerate conceptual understanding as may (though not invariably so) a high intelligence. There will be times when face value judgment can *prevent* anxiety, because implications are not understood, but it can also *provoke* it, because what is seen is perceived as being worse than it is. Thus a 3 year old on an intensive care unit may be relieved to see a sibling there at all without understanding (and so fearing) the attached equipment, yet a 7 year old, big enough now to know that people sometimes die in hospital, may be terrified when a parent has to be admitted, even for a trivial reason. Attendant adults should have enough insight to see things through the child's eyes and make the necessary interpretations.

As we look at the normal pattern of conceptual growth in childhood and then survey the world scene it would seem that nations and individuals are at a stage of arrested conceptual development. Hostility between races and nations acts out 'I am bigger than you'. The de-forestation in Africa has followed on people's regarding trees as firewood yet being ignorant of their implications for rainfall and soil erosion. Nearer home, we constantly hear of acts of violence, traffic accidents, or family breakdowns, many of which are based on a persistence of egocentricity. Perhaps the emergence of a spectator (rather than a participator) society prevents the personal interaction that would bring more thought for others. Acquisition of locomotor power, too (as at toddler level), may encourage its display. Is our own profession immune?

In neonatal care we have had to learn to de-centre and to include the family even in high dependency units. Face value judgment ('We must rush this baby off for surgery') has given way to deeper implications ('Family involvement must start first'). We are entering an era where insight is immensely important, for on the one hand is the attitude that painful problems should be despatched or ignored. Thus abortion for potential handicap is increasing, while facilities for those living with handicap are concurrently decreasing. (To send such children 'into the community' is only attractive at face value unless the implications of this have been anticipated and prepared for.) On the other hand, there is more and more that can be done in life threatening states to stave off the inevitable. Face value judgment could say that we must do it because it is there to do, but insight suggests that peaceful death, even in hospital, should not become an anachronism. That the public is not altogether happy with the way that medicine is going is made clear to us by the vogue for alternative forms of treatment We could be thwarting valuable experiences for patients and for ourselves by failing to see that pain may be necessary for growth (as in pruning) or correction (as in surgery). It cannot always be evaded, but neither should it be inflicted unsympathetically. If it is to bring optimal benefit there must be personal support during a painful process.

As individuals, doctors have probably been very much at risk for perpetuated egocentricity. The current revolt against paternalism and authority (albeit themselves the marks of an immature culture) may be creative in our own maturation, so that at last we take a greater interest in looking at things from the patients' viewpoints rather than our own. Untempered, technology could bring us into a total and fascinated preoccupation with the many new discoveries. Yet our very entry into a caring profession should mean that these exciting developments are tools towards the attainment of ideals in care, rather than their controlling us. We must not arrest at a 'me, too' level without weighing up whether what glitters really is golden or whether there are more worthwhile aspects requiring greater input that have passed others by. There is a real risk that, unless we think through these issues, we each become trapped by our own egos and, by definition, remain less mature than we ought to be. Even to be disease centred is not enough, for this could spell ongoing aggression at a time when to be patient centred would mean terminal care.

Spiritual awareness may emerge at times of crisis

When a family suddenly faces a harsh and inescapable diagnosis their former preoccupation with material prosperity and the accumulation of possessions and status proves to have been building on shifting sand. Parents often comment how they would give away their all if only this could save their child's life. Dying adolescents, minds now mature enough to think up huge questions, may start a search for spiritual wholeness as other hopes disintegrate Some have taken their parents with them on this search, to their mutual comfort.

Yet many a paediatrician with ears to hear is likely to have met at least one very young child for whom spiritual awareness is such a reality that profound statements of faith can be expressed without inhibition or embarrassment The child's *mind* is too young to grasp that everyone does not necessarily hold the same views, yet the child's *spirit* is so alive with the truths perceived that they unaffectedly spill over into ordinary conversation. One such 9 year old commented, quite naturally, how she could not have endured her bone marrow transplant without the Lord's help. Poetry and prayers, written in an isolation tent, give moving evidence that for her, spiritual life was a reality to be lived in terms of a committed relationship between her and the Lord God Almighty Himself. Her experiences of suffering had no doubt accelerated her intellectual and conceptual development as, even at that age, she was able to recognise the purpose of her treatment and make up her own mind to accept it. Yet she was untroubled by the doubts and agnosticism of older intellects and able to accept her troubles without resentment, though not without questions. For her, life's meaning was in relationships. As she put it, 'Without mum and dad I don't know what I would do. I mean I wouldn't have anyone to love or care for. Without you Lord my saviour, I wouldn't be able to go through with all my treatment.' She was no goody goody, but this added to the impact of her spiritual awareness on all who met her.

We live in a materially minded society, yet as care givers doctors may be assumed to have different priorities. Is this really so? It is possible for us to be so preoccupied with facts and figures, delighting in diagnosis, discussion, or debate, that we may be very clever—yet not wise enough to see that we are spiritually deprived and dwarfed. It is at the root of Judaeo-Christian beliefs that we are made in the image of God, which includes the idea of being in relationship with Him. Some of the old divines and older artists picture man gazing into the Creator's face with the same look of rapt adoration that a baby can give to a parent. Yet if this regard is not happening (through disbelief or disconnection) there will be a consequent spiritual failure to thrive and a powerlessness that leads to spiritual death, unless the relationship can be restored. It is the Christian message that this can be done—indeed, that divine initiative has been taken through the life, death, and resurrection of the Lord Jesus Christ to direct us toward contrition, forgiveness, and reconciliation with Him. To climb down hurts pride but is the lift off to new insights and changed priorities. To dismiss all this as a cranky creed or flight of fancy is to make a false deduction. Personal histories from all age groups affirm that spiritual life is one lived in a relationship that at last fills the previous God shaped gap. Struggling to fill this alone brings the alienation, infighting, and disease now pervading social, professional, and personal lives. It sometimes takes a crisis to see that, like all others, this supreme relationship needs nurture yet, like no other, is open to all

The pages of this journal are not the place for full discussion of this important topic, but perhaps our little leukaemic friend can have the last word:

> "The Lord loves us, we all should know that.
> He cares for us too.
> Buy a bible, read it and then perhaps people will understand
> Understand that the Lord does not want WAR. He want peace for his people. LISTEN TO THE LORD. He trust and loves us. AMEN."

My thanks to Edwin Hill for introducing me to his patient, Rachel, and to her parents for being so willing to share her writing with a wider world

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Archives of Disease in Childhood, 1987, **62**, 314–319

Correspondence

Growth and childhood asthma

Sir,

We read the recent article by Dr Balfour-Lynn with interest.[1] In this study the prepubertal height centile from a 'distance' chart of each individual child was extrapolated to the adult centile as an assessment of final height prognosis. It is the degree of epiphysial maturation, however, that determines the proportion of growth that has occurred and hence the height potential remaining, only 40% of the children in this study had an assessment of bone age. A further assumption was the use of development of pubic hair as a sign of the onset of puberty. Pubic hair, which is predominantly associated with adrenal androgen secretion, is not necessarily a sign of the onset of puberty Luxurious development of pubic hair is common in children with absent puberty secondary to hypogonadotrophic hypogonadism or gonadal dysgenesis

Figure 1 of this article depicted the timing of the growth spurt of a boy with asthma coincident with the onset of puberty One of the characteristics of puberty in boys is that the onset of the spontaneous growth acceleration occurs late in puberty, between genitalia stage 3 and 4[2] or more accurately at the attainment of a 10 ml testicular volume. Clearly, in Figure 1 the growth spurt was either unrelated to the spontaneous growth acceleration of puberty and perhaps due to 'catch up' growth secondary to effective treatment or the assessment of the onset of pubertal maturation was incorrect If the former was correct then the growth pattern was not due to delayed puberty; the latter would put the accuracy of the entire study into doubt. The data presented showed a loss of the harmony of normal growth and puberty, and this usually points to an endocrine abnormality.[3]

Such a longitudinal study should be an important contribution to our understanding of the growth of children with asthma, many of whom have delayed growth and puberty. The data presented and the errors in methodology, however, do not permit the conclusions that Dr Balfour-Lynn has made.

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Dr Balfour-Lynn comments.

It is intriguing to learn from the department made famous by Professor Tanner that children who faithfully follow one of the centile lines on his growth and development charts throughout the whole of their growing life cannot be considered to have grown normally In this study all 66 children were directly observed to do this up to at least 10 years of age, during the most severe period of their childhood asthma. Thirty five children continued to follow their chosen centile, whereas 30 were observed to have delay in the onset of puberty with a typical growth delay curve, even though in many this coincided with an improvement in their asthma and some, like the child in Figure 1, were actually free of symptoms Satisfactory catch up growth occurred in all these children. If this does not mean that asthma has no direct effect on growth, apart from indirectly by causing pubertal delay, then Professor Tanner's charts should no longer be considered acceptable standards and should be scrapped in every paediatric clinic in the country Support for this study was found, however, in 40% of these children from bone age predictions, a percentage highly acceptable to statisticians if not to Professor Preece and Dr Stanhope. Moreover, support was also presented from 91% of the parental heights, a fact ignored by them.

Pubic hair was mentioned in the assessment of puberty as Professor Tanner included it in great detail in all his charts [2] It was not noted to be the first sign of puberty in any of the boys, but it was in two girls If this is not acceptable as a sign of the onset of puberty then it means that the delay was even greater in the girls in this study

It is absurd to suggest that all this consistent data is destroyed by the chart of one boy. He had the greatest delay in the onset of puberty of all the children in the study and consequently the greatest centile loss in height during the deceleration in growth velocity Thus his pubertal delay curve was used as it was the most dramatic, though possibly some smoothing off by the medical artist has caused a little confusion His growth curve was especially interesting as he was one of the milder cases of asthma He was successfully treated with regular sodium cromoglycate from the age of 7 to 11 years, after which he rarely needed to use a salbutamol inhaler and was soon entirely free of symptoms There is no way his growth delay could be directly attributable to asthma or treatment Because of his pronounced pubertal delay, however, he was carefully observed as his parents were by then more concerned with this than his asthma Changes were first detected in his testes when seen at the age of 15·8 years (accuracy to within six months), which were obvious six months later When he was aged 16 8 years his genitalia had reached stage 3 and pubic hair was first noted A growth velocity curve shows that his peak height velocity coincides with this stage Marshall and Tanner, in the paper quoted by Professor Preece and Dr Stanhope, noted peak height velocity at stage 3 of puberty, though it occurred more commonly at stage 4 [2] Marshall and Tanner, however, were recording a series of children with normal growth, but in my experience of pubertal growth delay the greater the delay the more dramatic and earlier the growth spurt once puberty develops

In this study the methodology used for the assessment of growth, puberty, and bone age prediction have relied heavily on the work of Professor Tanner It is surprising that this is no longer acceptable to his old department.

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Screening for the detection of congenital dislocation of the hip

Sir,

We have read with interest the special report on 'Screening for the detection of congenital dislocation of the hip' prepared by an advisory committee for the Secretary of State.[1] It is recommended that the Ortolani/Barlow manoeuvre be carried out within 24 hours of birth, first the Ortolani procedure then the Barlow manoeuvre, 'with the thumb on the inner side of the thigh, backward pressure is applied to the head of the femur,' if a 'clunk' is obtained, 'the head is said to be subluxatable (dislocatable)' In other words, the hip is dislocated.

One of us (CHC) has noticed increasing laxity in the hip joint of an infant who has been repeatedly examined to show physical signs to junior medical colleagues In view of the risks associated with 'excessive manipulation of the hip joint', the advisory committee recommend that 'duplication of the examination by both midwife and doctor should be avoided Each maternity unit should determine its own policy in this respect to ensure that there is only one examination ' We submit that this advice is unrealistic and that in practice a midwife who discovers that she can dislocate a hip will continue to ask the resident doctor to confirm her finding and this will be checked by a paediatric registrar or consultant, or both The orthopaedic surgeon will probably carry out a further examination before applying a splint for what has become a recurrent dislocation.

The Southampton experience[2] of an increasing incidence of late congenital dislocation in an area practising enthusiastic neonatal screening with a reluctance to undertake unnecessary early splinting leads us to the conclusion that Barlow's manoeuvre in the first two days of life was converting normal joint laxity into established dislocation.

Barlow's manoeuvre does not distinguish between a normal hip and one that untreated will develop an established dislocation. Barlow showed that dislocatable hips are much more common in the first three days than later in the first week, and no cases of late dislocation were discovered in his infants who were first examined after the age of 3 days.[3]

We consider that during the first 48 hours of life when ligamentous laxity is so common great care should be taken *not* to dislocate a baby's hips either by swaddling with adducted thighs or by Barlow's manoeuvre. At this time clinical examination should be directed to discovering established dislocation by looking for asymmetry, apparent shortening of the femur, restriction of abduction, and a 'clunk' by the Ortolani procedure

We welcome the recommendation that repeated examinations for dislocation of the hip should be carried out throughout infancy because the evidence indicates that some dislocations are undiagnosable at birth and develop later

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Sir,

It has always been my impression that the chance of detecting congenital dislocation of the hip would be increased if the number of examinations by an experienced observer were increased In the recent article on congenital dislocation of the hip it is stated, 'In view of the risks associated with excessive manipulation of the hip joint, duplication of the examination by both midwife and doctor should be avoided.'[1]

What is the scientific evidence that there are such risks, and if there is indeed a risk what is its incidence?

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Dr Dunn comments:

Thank you for inviting me as a member of the SMAC/SNMAC working party under the chairmanship of Professor E Stroud to respond to these letters.

Drs Cheetham and Garrow's first point deals with a semantic problem Most abnormal hips at birth are of the unstable, subluxatable variety. They can be partially dislocated by backward pressure when the thigh is adducted and flexed We included the word 'dislocatable' in parenthesis because this term is in common use, even though such hips do not fully dislocate, as may be shown at necropsy.

Next they question our exhortation to avoid excessive manipulation of the hip joint, a point also raised by Dr Blumenthal The working party thought it important to emphasise that repeated examination *might* damage an unstable hip. While there is no clinical evidence to support or refute this belief, manipulation of the unstable hip at necropsy seems to increase hip instability The artery in the ligamentum teres is also vulnerable to trauma. Of course, it was appreciated that some repetition of hip examination was necessary as part of the ongoing screening process as well as to confirm the diagnosis in suspected cases

In their third paragraph Drs Cheetham and Garrow draw attention to the Southampton study, making reference to 'an area practising enthusiastic neonatal screening with a reluctance to undertake unnecessary early splinting leads us to the conclusion that Barlow's manoeuvre in the first two days of life was converting normal joint laxity into established dislocation.' My own interpretation is different and may be found elsewhere.[1]

Next your correspondents claim, on the basis of Barlow's 1962 study, that hips that become stable in the first three days of life will not dislocate later. If this was Barlow's experience then he was indeed lucky. Over the years I have observed 25 occasions when unstable hips became stable in the first week of life but subsequently required treatment for dislocation or dysplasia. This evidence was available to the working party and influenced the advice they gave. It will be published in due course.

For reasons just discussed Drs Cheetham and Garrow conclude that a baby's hips should not be examined during the first 48 hours of life. In my view this is dangerous advice and in the past is likely to have been responsible for many of the missed cases of congenital dislocation of the hip in babies that have been examined 'at birth'. At the same time they recommend that neonatal examination should seek signs of established congenital dislocation of the hip with limited abduction, shortening of the leg, etc. The working party also made this recommendation, though in fact these classic signs are quite rare at birth and are often associated with neuromuscular disease or severe prenatal oligohydramnios due to Potter's syndrome.

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Case conferences—for child abuse

Sir,

I think it is excellent that the *Archives* are publishing the beginnings of a debate on the issue of case conferences for child abuse.[1] The policy document on child abuse written by the Society of Clinical Psychiatrists requires response. In my view what is put forward about case conferences is one sided, and although they may represent many professionals' considerable anxieties about the system, there are other views and research.[1] The notion that case conferences are 'one of the most pernicious aspects of the (child abuse) procedures' requires challenge.

The notion that because case conferences are dangerously irresponsible because of having no continued existence in their own right is in my view an illogical and unhelpful statement. Professionals attend case conferences in role and they have to be personally accountable for any decisions that they help make. The current draft guidelines from the Department of Health and Social Services (DHSS) (April 1986) emphasise the responsibilities of conferences to 'produce and record clear, timely and reasonable recommendations to the agencies providing services.' Chairing should be 'by an experienced person, not directly involved in supervising the case at field level.' The responsibility for the management of child abuse is not placed on the case conference but on the agencies providing services and both through recommendations about chairing and key work social services departments are given this responsibility in a clear, precise way.

The second point is made that case conferences 'entail a gross breach of professional confidence. "Character assassination" may proceed without even the safeguards of a court of law' and that there is 'an unrestricted and irrevocable dissemination of defamatory allegations.' Yet on the other hand, inquiry after inquiry indicates that someone somewhere has the information that, if it had been shared, might have prevented the death of Jasmine Beckford. Hallatt and Stevenson have indicated that anxiety about such cases can be massive, case conferences can be contagious, and anxiety can increase and escalate and decisions can be made that are unhelpful and not thought through.[2] It is vital that good chairing takes control of what information is shared and is aware of group processes that can be destructive and those that can mobilise resources and concerns for the family. In my view the directive from the Home Office and DHSS,[3] which enabled the police and other professionals to take part in conferences and share information, has been a power for good, particularly when decision making is by consensus and respects the interests of the child without an unnecessarily punitive approach to the parents.

There is a criticism that case conferences are ineffectual because:

(a) Conferences cannot make crucial decisions, only highly trained professionals can.

(b) Even if people are there who can make such crucial decisions, they cannot do so unless they have had a proper contact with the case.

(c) Treatment cannot be offered unless the resources, both human and context wise, are known about.

(d) The case must be kept under review by a skilled professional.

In my view this series of arguments about case conferences is fallacious. It is true that often professionals who could make such assessments and therefore contribute to decisions are not present because they are not involved. Child and family psychiatric teams are not used sufficiently to help conferences think about the long term possibilities and needs of particular cases. If such a professional has made an assessment of the family, however, he should have no difficulty convincing the case conference of the needs of that family and the facilities available for it, because so often the court will have to be convinced of the same issues. Case conferences will be only too pleased if such a skilled professional offers to take on the supervisiòn and work with families and to use the conference for statutory professionals to report on progress or otherwise.

Drs Chapman and Woodmansey are really putting forward an impassioned plea that child and family psychiatric professionals do play a role in the management of child abuse.[4] As a result of having chaired most child abuse case conferences at Great Ormond Street for almost 20 years, I am in absolutely no doubt that the case conference system can be a highly effective way of bringing together information from many different sources, for integrating them, and beginning to answer the very questions that are raised in this article—that is, what is the need for protection, what is the need for work, who should carry this out, and how should it be supervised?

If we follow the DHSS guidelines I will gladly be handing over the chairing of such conferences to my social work colleagues. I hope I will continue to be present and that myself and my colleagues will still continue to do assessment work with families that I hope will assist conferences to make the sort of decisions that sadly do not seem to have occurred in Drs Chapman and Woodmansey's experiences.

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Sir,

The Society of Clinical Psychiatrists state that 'case conferences are inherently ineffectual' [1] I disagree. Child abuse case conferences are often ineffectual, but not inherently so

The case conference is like a ship, and its aim should be to reach a stated destination It is 14 years since the Tunbridge Wells study group made the child abuse case conference its cardinal recommendation [2] Is it any wonder that in that time the ship has acquired some barnacles? In addition, too many passengers have come on board

A case conference can exchange information, decide on registration and the nomination of a primary worker, and offer to the primary worker various forms of support

Bearing in mind this aim, I believe:

(i) Too many people attend, including those who have neither information nor an involvement with later management

(ii) Information is poorly given. It should be the aim to circulate written information before the day of the case conference

(iii) Far too much discussion takes place on the details of management. This can only be a matter for the primary worker and even if a valid decision is made at a case conference it is, as stated in the clinical psychiatrists' document, only valid for that moment. 'The decision cannot be made once and for all' [1]

(iv) Most minutes are inexpertly written, chairmen not being skilled as committee clerks The anxieties of professional workers can be discussed without being minuted Minutes should record the location and constitution of the meeting with the decisions taken

The case conference is a working method Without it professionals would again begin to act in isolation. Without it the choice of primary worker would be seen as arbitrary and as setting one group of professionals above the others

So I agree with much of the thinking of the Society of Clinical Psychiatrists but not with their conclusion. Without the case conference cooperation in child abuse would cease and the anxiety of professional workers would not be allayed

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The sweat test

Sir,

Dr Littlewood's annotation on the sweat test is to be welcomed as misdiagnosis of cystic fibrosis is a continuing and serious problem [1] We agree that most misdiagnoses can be avoided if experienced laboratory staff perform the sweat test with meticulous attention to detail and the results are interpreted in the light of the clinical findings.

Two points arise from the annotation, however, that we feel need further comment. Contrary to Dr Littlewood's opening paragraph, the sweat test in most hospitals does not usually imply measurement of both sodium and chloride. In our experience many centres measure only one ion, and there is a need to reinforce to both biochemists and paediatricians the importance of measuring sodium *and* chloride. Secondly, we do not support Dr Littlewood's conclusion about the use of pancreatic function tests. Diagnostic difficulty is more likely to occur in the 10% of patients with cystic fibrosis who have adequate exocrine pancreatic function, and it is in these patients that further investigation of pancreatic function may not be helpful

In our own prospective study of 344 patients over two years 441 sweat tests were performed at our hospital and only nine fell into an equivocal group One of these nine was subsequently confirmed to have cystic fibrosis. The other eight patients all had sodium values considerably higher than the chloride values; they all had normal pancreatic function as judged by normal results of faecal chymotrypsin and *para*-aminobenzoic acid tests and, in two patients, normal secretin-pancreozymin stimulation tests It was the interpretation of the results of their sweat test together with their natural history that excluded the diagnosis of cystic fibrosis rather than reliance on normal pancreatic function tests We think that it is misleading to suggest that demonstration of abnormal pancreatic function is the gold standard for the confirmation of the diagnosis of cystic fibrosis in equivocal cases. Until deoxyribonucleic acid technology can identify the gene the diagnosis of cystic fibrosis will depend on the correct interpretation of both sweat sodium and chloride in the light of the clinical findings, with *support* from investigation of pancreatic function

Reference

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Dr Littlewood comments.

Dr Green and colleagues observe that many laboratories do not measure both sweat sodium and chloride; thus, in marginal cases, it is impossible to determine whether the chloride is higher than the sodium. While I would support the value of their observation that the chloride is commonly higher than the sodium in patients with cystic fibrosis who have marginal values and agree with their advice to measure both electrolytes, the higher chloride value in patients with cystic fibrosis can only be regarded as useful supportive evidence for the diagnosis.[1]

I would not accept that 'it was the interpretation of the results of the sweat test together with the natural history that excluded the diagnosis' Unfortunately, Dr Green and colleagues provide little evidence that their small series of children with marginal results of the sweat test did *not* have cystic fibrosis Certainly, normal results of a *para*-aminotenzoic acid test and faecal chymotrypsin test cannot be taken to exclude a minor degree of pancreatic involvement

All evidence to the present suggests that demonstration of normal pancreatic function by pancreozymin secretin stimulation, particularly a normal bicarbonate secretion, remains the most reliable supportive evidence for the exclusion of cystic fibrosis [2 3]

Our experience at the Leeds regional cystic fibrosis unit, derived from comprehensive assessment of over 200 patients with cystic fibrosis, in addition to many referred where the diagnosis was in doubt, suggests that individuals with cystic fibrosis who have marginal sweat electrolyte values usually have additional supportive evidence—for example, pseudomonas lung disease, obvious malabsorption, and pancreatic abnormality. Furthermore, there seems to be no direct correlation between the degree of sweat electrolyte abnormality and either the severity of the pancreatic lesion or the clinical score.

Thus I would reiterate the suggested diagnostic criteria as previously stated.[4] While the relation of sodium to chloride is a valuable observation when a reliable sweat test gives a marginal result, confirmation or exclusion of the diagnosis must thereafter depend on findings other than the sweat test.

It should be re-emphasised that the common diagnostic difficulties and not uncommon actual mistakes usually result from an incorrect determination of the sweat electrolytes by the biochemist and an uncritical acceptance of the result by the clinician who also fails to show any gastrointestinal lesion or request a confirmatory sweat test at a later date

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Small for dates babies: are they really a problem?

Sir,

Doctors Jones and Roberton conclude, in their recent good paper, that small for dates (SFD) babies of 37 weeks' gestation or more pose few neonatal problems.[1] That this is so in their neonatal unit is because of the unit's admirable and justified reputation and of its surrounding population, in general, with a high standard of antenatal and other health care

The only reason I write is lest the title of their paper masks an important background that has two basic features. Firstly, of infants born with low birth weight in the developing world, it is estimated the component of SFD infants over preterm infants is nearly three times greater than that in the developed world (80% as opposed to 30%) This suggests that a reversible condition exists. prevention of intrauterine growth failure. Under conditions in the developing world many of these SFD infants contribute to very high perinatal and infant mortality and morbidity.

Secondly, the important question of outcome Experienced neonatologists, like these authors, know that clinically there are broadly two kinds of SFD infants those that 'do well' and those who do not Recent work has carried this further.[2] Ultrasonography and anthropometry suggest that proportional fetal smallness, with small head size, in fetuses destined to be SFD infants leads to those who exhibit poor postnatal catch up growth, including that of head (and brain?) size. By contrast, those fetuses who are disproportionally small (with 'normal' size fetal heads) seem to exhibit good postnatal catch up Perhaps, then, there is a distribution curve for outcome—the non-'catch uppers' at one end, with the vigorous 'catch uppers' at the other.

I suspect, because of the reasons I have suggested, that if Doctors Jones and Roberton followed their sample of SFD infants they would find them to be at the latter end.

May I repeat that my comments are the opposite of criticism of their good paper; only that their title might lead us to complacency about all SFD infants

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Drs Jones and Roberton comment·

We thank Professor Falkner for his interest in our paper. Our study was not directed, however, at the problem he is addressing. In fact, there is much to suggest that the 'proportional' small for dates baby actually poses fewer immediate neonatal problems than the one with overt fetal malnutrition We agree our results should not be applied in developing countries

We acknowledge that the proportionally small SFD baby may do less well in terms of growth and even long term neurological development, and indeed that it may well be modifiable by improvements in many aspects of the maternal nutritional and social environment. Nevertheless, these babies do extremely well in the neonatal period, and, sadly, there is nothing that the neonatal paediatrician can do to influence their long term outcome.

Interaction between chloramphenicol and acetaminophen

Sir,

It is unfortunate that the study by Spika and colleagues on the interaction between chloramphenicol and paracetamol[1] did not include data on the pharmacokinetics of chloramphenicol after treatment with paracetamol had been stopped. The clearance of chloramphenicol has been shown to increase during a course of treatment from 268 ml/h/kg on day 2 to 383 ml/h/kg on day 10 [2] These incidental findings were subsequently confirmed in a carefully controlled study of 10 children who were examined on two separate occasions while remaining on the same intravenous dose of chloramphenicol [3] The mean elimination half life for chloramphenicol fell from 3·0 hours to 2 3 hours during the course of treatment. It is therefore possible that the changes in chloramphenicol pharmacokinetics observed by Spika and colleagues were unrelated to paracetamol

It is regrettable that the editors decided not to use the English language in a British journal and hence paracetamol was described as acetaminophen and rifampicin as rifampin.

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Archives of Disease in Childhood, 1987, **62,** 320–323

Book reviews

Craniosynostosis. Diagnosis, Evaluation and Management. Edited by M M Cohen Jr. Pp 606: $148·50 hardback Raven Press, 1986.

The craniosynostoses are not common conditions but as plastic surgeons, neurosurgeons, and others get together to form craniofacial teams more cases are being seen who might not otherwise have been considered candidates for surgical treatment for either cosmetic reasons alone or to avert neurodevelopmental problems due to cerebral compression

This book achieves a remarkable balance, not only providing an excellent and comprehensible overview of the subject but also by going into certain technical areas (surgery and genetics, for example) in such depth that even an expert will have much to learn This must be due in great measure to the skill of the editor, Professor M Michael Cohen Jr Already well known in neurosurgical circles for his articles on the genetic syndromes associated with craniosynostosis, here he provides almost half the text himself, while the remainder is entrusted to a highly selected and prestigious group of contributors. Among these I would pick out Ronald J Lemire (Embryology), Thomas P Naidich (Radiology), John A Jane (Neurosurgical treatment), and, the doyen of craniofacial surgeons, Paul Tessier. But this list should not lead one to assume that the other chapters are not of a high calibre and I would select Sven Kreiborg on the 'post natal growth and development of the craniofacial complex in premature craniosynostosis' as an excellent review of this thorny subject, where the possibility that early surgical intervention to the skull base sutures will allow the face to grow forwards normally in the future is still hotly debated Dr Kreiborg's view (and I would agree with him here) is that the growth of the facial structures is more dependent on the patient's syndrome and the primary impairment of facial growth that implies than to any restriction placed on it by the prematurely fused sutures of the skull base and vault.

Overall, I would call this a model textbook The production with regard to its photographs and drawings is excellent. Where knowledge is scanty and opinions count for more than facts its views are moderate Yet where order must be imposed on areas of chaos (as in Professor Cohen's dealings with the syndrome hunters) it has the ring of true authority

RICHARD HAYWARD

Clinical Paediatric Nephrology. Edited by R J Postlethwaite. Pp 495· £35·00 hardback. Wright, 1986

This is a first rate, comprehensive textbook that covers the whole range of renal medicine and includes three useful chapters on urological problems There are nearly 40 authors, well known for their contributions to paediatric nephrology, from both sides of the Atlantic

Separate chapters are devoted to major presenting symptom complexes and signs—namely hypertension, haematuria, proteinuria, oedema, enlarged kidneys, wetting, and infection. These guide us logically through causes, investigations, and management Glomerulonephritis is well covered, and management of acute and chronic renal failure is described in detail There are two excellent chapters on those difficult subjects, renal tubular disorders and cystic disease, written from the clinical point of view

Discussion of urinary tract infection includes the clinical features at different ages, methods of urine collection, and the importance of symptomatic and asymptomatic bacteriuria Investigations and management are described fully, but not all paediatricians would agree with the recommendation that invasive investigations, intravenous urography and micturating cystourethrography, be performed in all children under 5 after the first infection. Ultrasound examination, which is completely painless and almost as informative, is now an acceptable alternative, as mentioned in a later section of the book

The difficult problem of treating the neuropathic bladder, and numerous abnormalities that require the attention of the paediatric urologist, are described lucidly, management being summed up by the adage, 'All you can do is kill the germs and fix the plumbing' An excellent review, liberally illustrated, of imaging techniques together with chapters on growth, bone disease, homeostasis, and investigation of renal function complete the contents

The book is clearly written and the illustrations are excellent. The numerous references are completely up to date, some as recent as 1986, and the price is modest It will serve as both a guide to generalists and a reference text for specialists I strongly recommend it.

MARTIN MONCRIEFF

Childhood Epidemiology. *Br Med Bull* 1986 **42** (2) Edited by E D Alberman and C A Peckham. Pp 219. £16·00 softback Churchill Livingstone, 1986

The authors' stated aim is to show how recent developments in childhood epidemiology have grown out of an awareness that epidemiological studies in childhood must relate to genetic and environmental factors that influence growth and development as well as to the natural history of disease. The authors achieve their aim but they also provide a very valuable, tightly packed mass of information about the aetiology and distribution of the whole range of disease in childhood The chapter on infections is a model of simplicity and clarity Unfortunately, not all of the subjects lend themselves to a similar approach, and although the information is always there, the reader sometimes has to hunt to find the message.

About half of the contributions are concerned with aspects of growth and development. As well as excellent accounts of problems of hearing and vision these provide a very useful discussion of patterns of morbidity and mortality at all ages of childhood and include an important section on special and intensive care for neonates The chapters on physical and on behavioural and intellectual development provide useful critical discussion of methods as well as the usual facts. This part of the book, together with the chapters concerned with the effects of environment and with prevention, should be required reading not only for community paediatricians but for politicians, general managers, and all who have responsibility for the allocation of resources

The remaining chapters provide lucid accounts of the aetiology of respiratory diseases, hypertension, disorders of the gastrointestinal tract, and the urogenital, endocrine, haemopoietic, and musculoskeletal systems Their contents will be of great interest and value to the general paediatrician and to all those who are preparing for higher examinations, but one suspects that the contents of each individual chapter will already be familiar to the appropriate sub- or supraspecialist who has kept up with his subject.

This is a book that contains something for everybody and a copy should be available in every departmental library

J A YOUNG

Padiatrische Differentialdiagnose: 2. uberarbeitete Auflage. By V M Hertl. Pp 661. DM 248 hardback George Thieme, 1986.

The differential diagnosis of diseases in childhood is usually discussed briefly under individual headings in most paediatric textbooks large and small. There are also a few books popular with those preparing for examinations that list signs and symptoms. Some 'paediatric case studies' usually complete the collection of texts on general paediatrics in any medical bookshop or library This 660 page hardback, however, is different as it discusses the phenomena of diseases rather than the nosology and the author would, therefore, like to see it used in conjunction with a standard textbook

Signs and symptoms are discussed (but often only defined or listed) in six sections There are all the obvious chapters on pain, dyspnoea, impaired consciousness, abnormal gait, stridor, vomiting, abnormal bowel motions, and 13 chapters on various body regions from intradermal and subdermal signs to bone and joint disorders There is notable emphasis on psychosomatic and psychiatric symptoms, including sleep disorders, vertigo, lethargy and depression, restlessness, learning difficulties, behaviour disorders, autism, and homosexuality. There are brief chapters on age related problems, life threatening situations, and an appendix with tables and normal values, as well as a very detailed index

Having used this book for several weeks now I am not sure how much it has helped me in the differential diagnosis of common or rare diseases I found the approach often too theoretical and sometimes old fashioned There are, for instance, 18 pages on heart diseases, although if faced with a cyanotic newborn the non-specialist would have great difficulties in finding advice about how to arrive at a provisional diagnosis There are a few gaps and omissions For instance, phonocardiographic findings are discussed but cardiac ultrasound is not mentioned Child abuse is not covered adequately and I could not find the German equivalent of 'toddlers' diarrhoea' in the section on chronic diarrhoea

Who is this book aimed at? It is of limited use to the more experienced paediatrician, although he might like to use some of the excellent graphs and high quality pictures for teaching purposes, the medical student would presumably be overwhelmed by both the wealth of the information and the price of the book It is probably the junior doctor and general practitioner with a special interest in paediatrics who may enjoy reading it most For an English translation to be successful this, in many ways excellent, book would have to be shorter, more practical in its approach, more up to date in some aspects, and cheaper to purchase

MARTIN BECKER

Advances in Pediatric Infectious Diseases. Vol 1 Edited by S C Aronoff, W T Hughes, S Kohl, W T Speck, E R Wald Pp 192. £24·00 hardback Year Book Medical Publishers, 1986

This is the first in a series intended to provide concise and complete reviews in a rapidly advancing field of paediatrics. The aim is to give information useful to the clinician in his daily work and to couple this with extensive reference for those who wish to delve further.

By virtue of its position as volume 1, it is perhaps unfair to direct criticism at its content. There is, for example, a very pedestrian account of an old subject, infectious diarrhoea, a chapter that falls into the trap of trying to be all inclusive and succeeds only in saying a little about a lot, and yet nothing on paediatric human immunodeficiency virus infection Indeed, many of the chapters are more a review of their subject, past and present, than a tightly written account of 'advances' in its treatment or in our understanding of it It is perhaps significant that the cover title is so designed that 'Advances in . . ' recedes in white and 'Pediatric Infectious Diseases' stands out in gold!

There is, none the less, a very interesting and lucid account of Lyme disease and Epstein-Barr virus infection, a logical approach to the often met problems of bacteraemia in the febrile child, and discussion of varicella zoster infections in their various settings Other disparate areas covered include shunt catheter infections, cytomegalovirus in the neonate and infant, group A streptococcal pharyngitis, and rapid viral diagnostic techniques The latter chapter would not unfortunately leave most readers with a clear understanding of the various techniques available, perhaps because it assumes a large degree of basic laboratory knowledge and gives too cursory a summary.

In conclusion, this is a useful book but suffers from the problems of a multi-author text in having varying standards in different chapters None the less, for libraries intent on collecting the series, it is a worthwhile first entry. As a one off buy I would look elsewhere to spend £24·00.

S P CONWAY

Recent advances in epilepsy. No 3. Edited by T A Pedley and B S Meldrum Pp 315. £38·00 hardback Churchill Livingstone, 1986.

This is the third volume in a series conceived as a cumulative textbook representing the state of the art in the field of epilepsy. The previous volumes had much to interest paediatricians, and the present one is no exception Of the 14 reviews, three are exclusively concerned with children—namely, those on the benign focal epilepsies (Lerman and Kivity), nonconvulsive status epilepticus (Stores), and the Aircardi syndrome (Chevrie and Aircardi) There is a concise critique of the genetics of epilepsy (Hauser and Anderson), including an appendix of 140 genetic syndromes with McKusick numbers, and a more detailed look at the progressive myoclonus epilepsies (Berkovic and Andermann) Chapters on sleep and epilepsy (Baldy-Moulinier) and ambulatory electroencephalographic (EEG) monitoring (Ebersole and Bridgers) define indications for all night polygraphy and cassette recording The value of precise clinical descriptions, videorecording, and specialised EEG investigations are emphasised in two reviews that clearly distinguish complex partial seizures of temporal lobe (hippocampal-amygdalar) origin (Wieser) and frontal lobe origin (Quesney). Aspects of treatment covered in this volume include a summary of toxic effects (Schmidt) and updates on barbiturates (Prichard and

Mattson) and ethosuximide (Fromm and Crumrine). Finally, there are reviews on the complex relation of sexual disorders to epilepsy (Ribak), the latter strongly based on animal experimental studies

Paediatric libraries should have these three volumes, which form a unit. Those doctors with a special interest in epilepsy will undoubtedly want to have them on their own shelves

J B P STEPHENSON

The Treatment of Children by Acupuncture. By J Scott. Pp 199 softback. The Journal of Chinese Medicine, 1986

This book is mainly a practical handbook for those already practising acupuncture and familiar with traditional Chinese medicine and is, therefore, of limited value to those who are not, for whom the terminology is largely incomprehensible, despite a limited glossary Dr Scott has several qualifications, though not medical, and practises acupuncture for children in a Brighton clinic.

The opening chapter reminds us of some of the rich wisdom in ancient Chinese sayings, but the author goes on to give us (from his own experience supplemented by translation from Chinese texts) some quaint explanations of disease: 'a red tip to the tongue always denotes mental irritation' There are many dogmatic statements that have no foundation in medical facts ('inoculations commonly cause hyperactivity and retarded growth'), and despite believing that alternative treatments can be complementary to orthodox medicine, I find it hard to take Dr Scott seriously It is a relief that in occasional diseases such as pneumonia and convulsions a combination with Western medicine is recommended

Apart from increasing general awareness of different approaches to disease, this book would be of little value in a paediatric library.

JOSEPHINE HAMMOND

Advances in International Maternal and Child Health. Edited by D B Jelliffe and E F P Jelliffe. Pp 227· £22·00 hardback Clarendon Press, 1986

To attempt to cover a balanced selection of the recent publications on maternal and child health in one volume sounds an impossible task. The editors have made a creditable attempt and this book, the sixth in a yearly series, inevitably reflects their orientation—towards breast feeding, nutritional assessment, and the socioeconomic and political aspects of maternal and child health. All the contributors bar one (an Australian) are from the United States, which is a disappointment in a book with this title.

The nine chapters are mostly clear and relevant reviews of controversial topics. In addition to those mentioned below, the selection includes an update on the measurement of malnutrition; two chapters on breast feeding; appropriate technology in perinatal care, and the cost benefits of immunisation programmes The first two reviews look at international political issues; as the editors point out in their preface, "Family health . depends as much on politics as on the invasiveness of bacteria and immunity". Eisenbud and colleagues review the effects on children and adolescents of the threat of a nuclear war It is now well known that "thoughts of nuclear annihilation have penetrated deeply into the consciousness of children", but it is sad to hear that most do not talk to their parents about their fears. Far more Soviet than American children believe that a nuclear war is preventable. The Soviet Union does not come out so well from the next chapter, which examines that country's failure to publish infant mortality statistics since 1974 Field depends more on speculation than on facts in listing the factors that could cause the assumed rising mortality These include a high birth rate in the disadvantaged rural areas, a deteriorating medical system, maternal alcoholism, and the effects of the arms race on health care All these factors are also present in many other countries, and certainly defence expenditure has been shown to be related to infant mortalities A more scientific approach is merited, however, in a book of this authority.

The two other chapters I found most useful were a review of iodine deficiency disorders and an account of the effects of the street food trade on women and children We learn that iodised oil by injection is the best means of prevention of goitre and is administered by 'barefoot doctors' in China· would that such a system could be introduced for immunisation in this country Why not put iodine in the bread and the water? It can be done, Hetzel tells us, but only where the population has access to such luxuries . . .

Street food trade is an understudied part of the 'health system' and could merit review in London as well as in the Philippines, though the results might be less positive It was a surprise to me to learn from Cohen that the street food trade is of value (1) because it contributes to the urban economy, (2) because it saves cooking time for working women, and (3) it is even nutritious—because traditional foods cooked in scarce oil are often used.

Overall, the book is a valuable anthology but I would like to see a wider range of authors and subjects included, the delivery of primary health care and the first line management of common acute diseases could profit from coverage It should be in the library of all internationally orientated paediatric departments

TONY WATERSTON

Foundations of Developmental Genetics. By D J Pritchard. Pp 372: £14·50 softback, £33·00 hardback Taylor and Francis, 1986

This book provides a detailed introduction to developmental genetics and is intended primarily for undergraduates. It will be particularly useful for doctors and medical students, however, as it emphasises the close links between embryology, genetics, and molecular biology and assumes only a basic knowledge of transmission genetics, biology, and biochemistry. It is well written, beautifully presented, and contains many clear diagrams There is an extensive selection of references at the end of each chapter, leaving the prose uncluttered. Many of the examples are taken from the animal kingdom and the medical implications of variations in embryological development and genetic expression are rarely mentioned. Viruses are omitted completely.

The book begins by discussing the differences between prokaryotes and eukaryotes The method of initiation of cytodifferentiation follows and then a description of the destination of entoderm, mesoderm, and ectoderm in a developing vertebrate In the chapter on embryonic induction there is a detailed explanation of the development of the eye and the fate of the neural crest. The chapter on cytoplasmic and extracellular controls emphasises that natural selection acts on the phenotype, which is the product of genotype and environment. The structure and function of deoxyribonucleic acid and ribonucleic acid, and the genetic code and its translation, are carefully described Theories regarding gene amplification, deletion, and expression are discussed and also the genetic basis of antibody diversity.

The glossary at the end is exceptionally clear and concise, and in the conclusion there is an interesting guide to the 'epigenetic space' existing between the genotype and phenotype, and a new epigenetic theory of evolution is proposed.

The field of genetics is expanding rapidly and as an increasing number of diseases is understood at a genetic, or even a molecular, level doctors in all fields will require a good working knowledge of developmental genetics. This book provides an enjoyable way of acquiring that knowledge and at £14·50 for the softback edition is very good value.

FRANCES FLINTER

Clinics in Gastroenterology. Paediatric Gastroenterology. Vol 15 Edited by J A Walker-Smith. Pp 203· £13·50 hardback W B Saunders, 1986

The publication of this book provides an opportunity to drive a further nail into the coffin of the idea that paediatric gastroenterology is all colic and constipation. In the nine years since a previous issue of 'Clinics in Gastroenterology' was devoted to paediatrics, there has been a remarkable expansion in both clinical and academic activity in this specialty, which is well reflected in this volume edited by John Walker-Smith.

In particular, it is gratifying to note the arrival of nutritional care, in the primary management of Crohn's disease and cystic fibrosis, for example, as a discipline not best left to the nursing staff or to colleagues practising in developing countries There are two excellent chapters on infective diarrhoea, both of which are lucid and succinct; Peter Milla reminds us that without motility the gut is but a ship without sails. Although John Walker-Smith's contribution on food sensitive enteropathies is as well written as one has come to expect, I did just wonder if the most exciting days of this topic are in the past For me, the chapter on the emotional sequelae of inflammatory bowel disease was a gem and of relevance to all who treat chronic disease in childhood, whatever their special interests. Sadly, I had just read the chapter on antigen handling by the same author in another book; they were identical.

I suppose that editors are allowed to be idiosyncratic There is perhaps a place, however, in a landmark publication like this, for an authorship that more truly reflects the worldwide interests and expertise in paediatric gastroenterology. A chapter covering all, rather than just one, of the newly recognised causes of protracted diarrhoea in infancy may have been more helpful, and an update on liver transplantation would have lent a desirable topicality. I was a little disappointed that the relation between paediatric gastroenterology and hepatology and the developing world was not more formally acknowledged, although these quibbles are probably but a sign of how much the editor was spoilt for choice

We all say that our own specialty is rapidly expanding; I hope that paediatricians will read this book and judge for themselves

I W BOOTH

Archives of Disease in Childhood, 1987, **62,** 324

British paediatrics

Future development of the public health function and community medicine

The Department of Health and Social Security (DHSS) has set up a committee of inquiry into the future development of the public health function and community medicine In its evidence to this committee the British Paediatric Association (BPA) emphasises the role of the Association and its members in the field of public health and reaffirms its commitment to an integrated comprehensive child health service.

The BPA considers that paediatrics and community medicine must work together in partnership on the administrative aspects of a comprehensive child health service, with consultant paediatricians providing the clinical leadership. Paediatricians working primarily in the community should undertake some administrative duties in addition to their clinical functions. Paediatric advice should be sought on certain aspects of planning, such as the use of hospital resources and the most appropriate types of service for the handicapped child.

Splitting the child health service into hospital and community divisions is inimical to the development of an effective comprehensive service. Preventive and curative services should therefore be integrated and health districts should have a single paediatric and child health division to which all specialist medical personnel in the child health service should belong. At primary care level general practitioners and clinical medical officers must increasingly come together. The criteria on which the allocations of resources is based should include outpatient and day care services (incorporating those for children with physical and mental handicap) and the number of inpatient beds for children and their occupancy.

Postgraduate training for community child health medical staff is essential at both primary and secondary care levels if the child health service is to be improved. This implies support for academic departments of child health, which are best able to determine training requirements and provide the training.

The main recommendations of the BPA are:

(1) Integration of the child health service should be promoted more actively.

(2) There should be at least one consultant paediatrician in community child health per district, building up to two or three in due course.

(3) Facilities should be provided for improving the postgraduate training of child health doctors.

(4) The allocation of financial resources for the child health services should be based on more appropriate criteria and the resources should be made available in a single budget rather than by funding hospital and community services separately.

A D M Jackson

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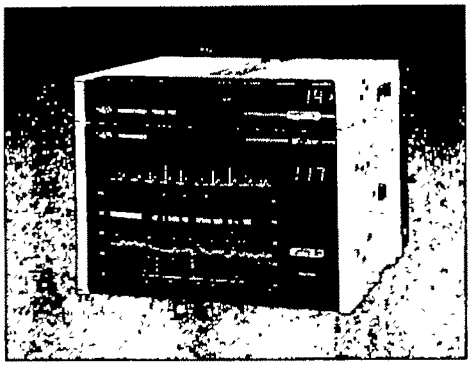

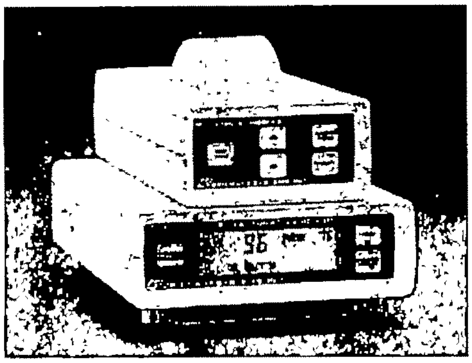

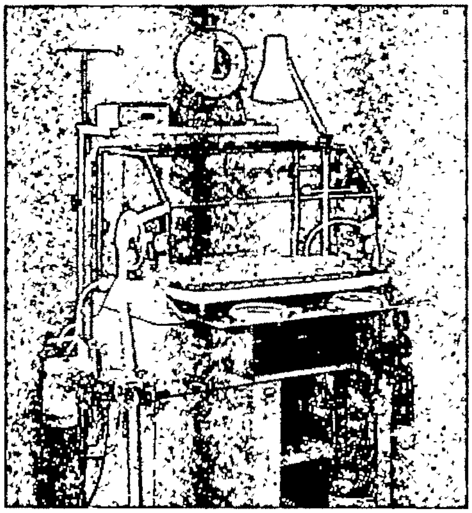

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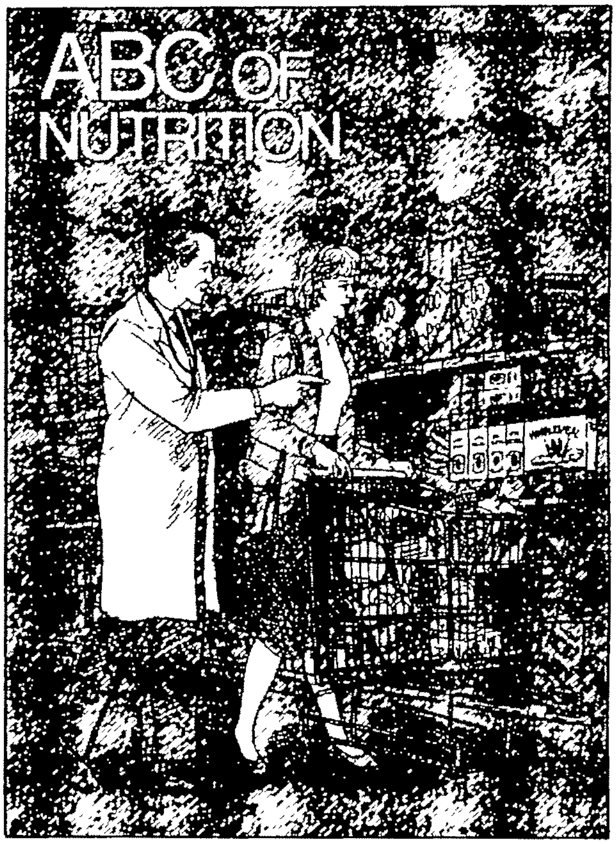

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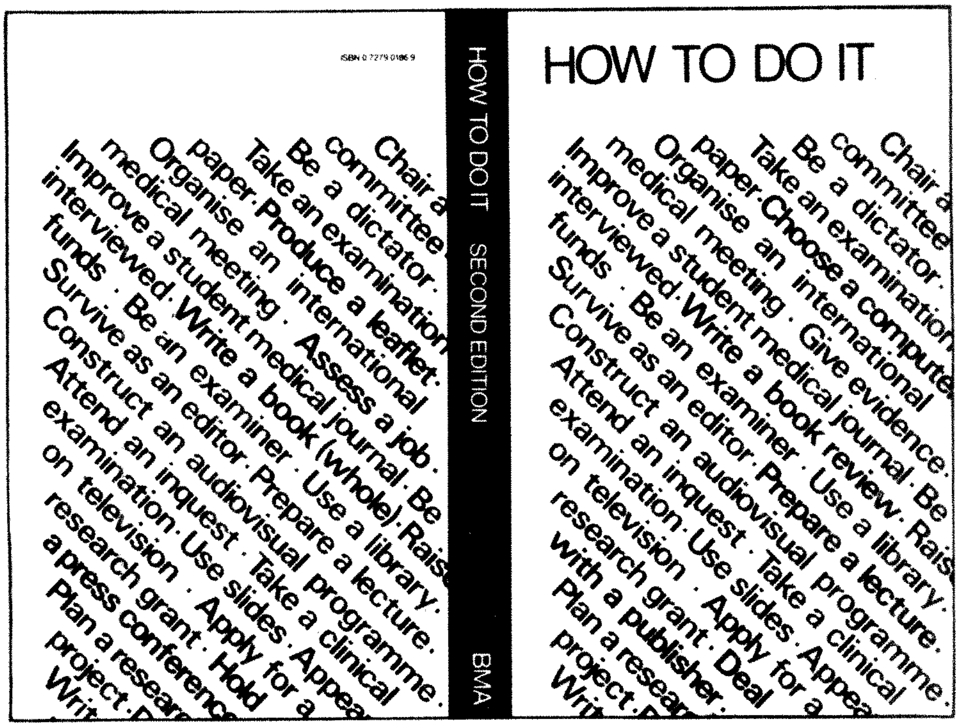

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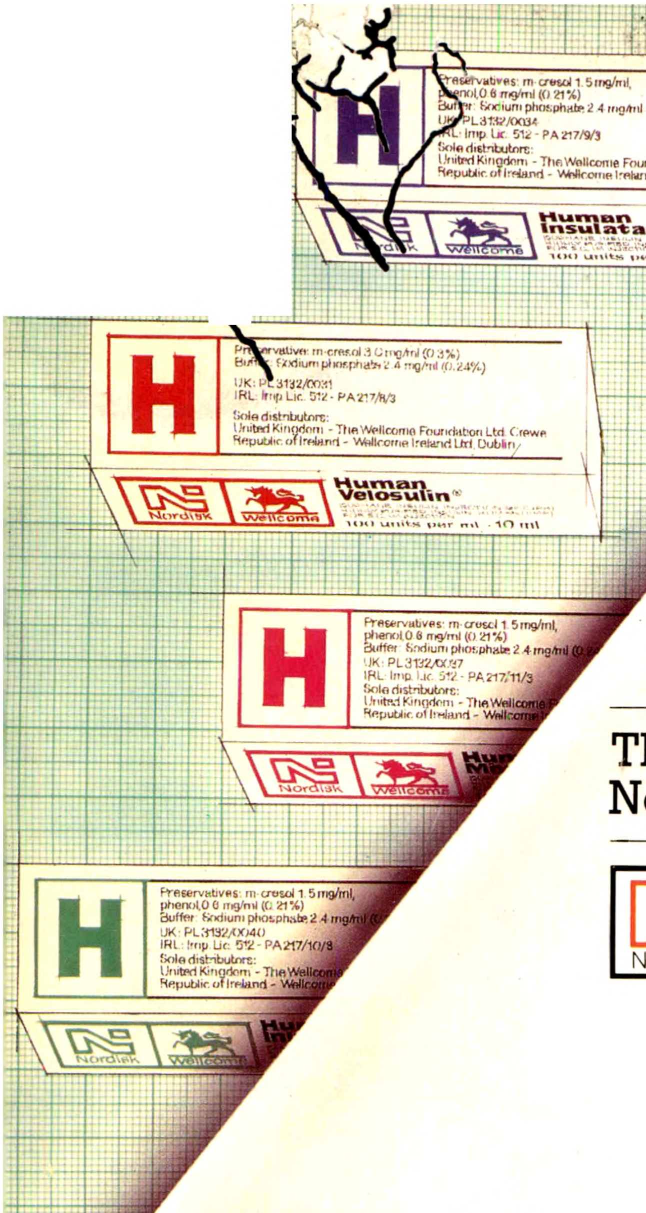

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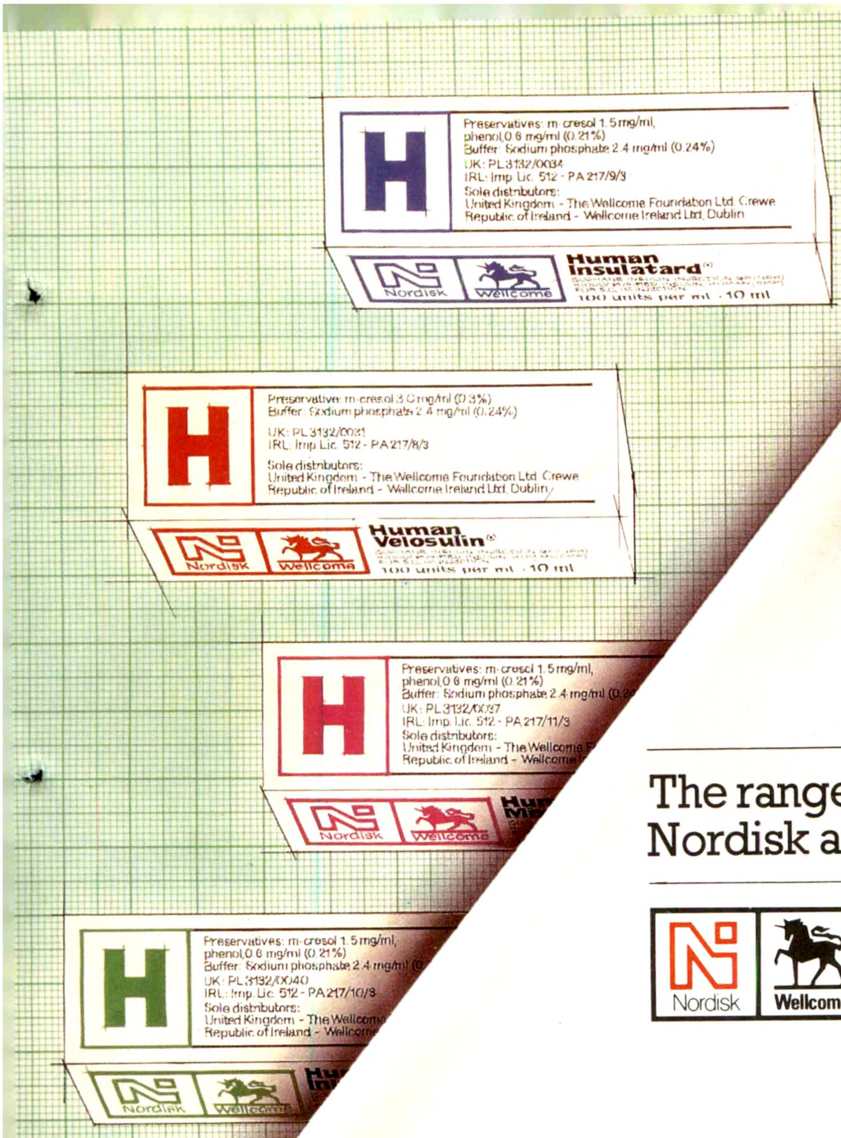
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Annotations

Liver transplantation—a role for all paediatricians

In the last three years there has been an encouraging improvement in the success rate and availability of liver transplantation for children. One year survival figures of between 50 and 90% are being reported from an increasing number of centres in Europe and the United States. If all paediatricians were concerned about the plight of children with liver disorders the position would be much better.

The current problems were assessed at a symposium on medical, surgical, and paramedical aspects of liver transplantation in children in Louvain, Belgium, in October 1986.[1] Four years ago only the Pittsburgh Service under the direction of Professor Tom Starzl had appreciable experience of liver transplantation in children.[2 3] At the Louvain meeting results were reported from seven other services in which between 23 and 44 children had had liver grafts. Altogether, 68% of 243 children were alive at the time of reporting, three months to three years after grafting. The age at grafting ranged from 14 days upwards.

The experience of the Cambridge/King's College Hospital Paediatric Liver Transplantation service, an extension of the adult programme directed by Professor Sir Roy Calne and Dr Roger Williams,[3 4] was similar to that reported from other centres and illustrates current short term results.[5] Eighty four children were assessed for liver transplantation. Eighteen, mainly infants with extrahepatic biliary atresia were not accepted because of features that made successful transplantation unlikely. Five had irreversible disease in other systems, seven had blocked portal veins, and nine weighed less than 10 kg, a size at which technical difficulties may be anticipated but also at which donor livers of suitable size are rarely available. Four children were withdrawn from the programme by their parents. Nine died before a donor of suitable size or compatible blood group could be found. Nine were awaiting transplantation and nine had been accepted for liver transplantation but were sufficiently well at the time for this to be postponed.

Thirty five have had liver grafts. Of these, 17 had biliary atresia, eight had cirrhosis after hepatitis in infancy, five had fulminant or subacute hepatic failure, three had liver tumours, and two had metabolic disease. Fourteen died, nine in the first two months mainly from primary graft failure or vascular thrombosis, later deaths being due to rejection, infection, or dissemination of malignant disease. Two, with a normally functioning transplanted liver, died of disease in other organs. Three of the survivors have had a second liver transplant. Most are engaged in normal activities for their age, growing and developing satisfactorily with complete regression of features of cirrhosis. Three do have considerable hepatobiliary problems, which may require retransplantation.

The condition of 65 children from a group of 90 children transplanted in Pittsburgh between 1981 and 1984 was particularly encouraging.[6] All had been followed up for more than two years. Most were leading normal lives for their ages, 77% were attending school in a normal fashion, and 75% were showing normal or accelerated growth rates, although 40% did have slightly abnormal aspartate aminotransferase activities up to 2·5 times the upper limit of normal. An equal number had increased blood urea concentrations, a side effect of treatment with cyclosporin.

Professor Starzl, analysing some aspects of his experience of over 600 liver transplants, 240 of which had been performed in children (365 were performed in 1985), emphasised that there are still major technical and biological problems to be overcome if the one year graft survival rate of 54% and the five year graft survival rate of 45% were to be improved.[7] Only the Pittsburgh service has sufficient donors available to offer retransplantation to an appreciable percentage of patients in whom the first graft fails. Such patients are given priority when a donor liver becomes available: hence the 90% one year survival rate in Pittsburgh. Lack of donors is a particular problem below 1 year, the age at which most potential recipients die. Professor Otte's group has shown that using part of the liver of an older child[8] is a feasible alternative.[9]

An important contribution to the welfare of children with chronic liver disease has been the development of parents associations—for example, the Michael McGouch Foundation against Liver Disease in Children—usually started by individual parents driven by the plight of a child dying of liver disease. These associations provide invaluable emotional and social support for parents, as well as striving to improve services. To obtain the services the children require these parents have often had to add to their problems[10] by obtaining 'media exposure'.

What can all paediatricians do to improve the situation? When faced with the hopeless situation of a brain dead child on a ventilator, remember that another child will be facing death from advanced kidney, heart, or liver disease. The only hope for that child and the family will be a grafted organ. The only comfort for the parents of the dying child on a ventilator may be in helping other parents who without a donor would also lose a child. Currently, the longest survival with a good quality of life after liver transplantation is 17 years.[7]

The second task is less dramatic: making transplantation unnecessary for most infants with biliary atresia by offering expert surgery by 8 weeks of age. This has been achieved in Japan. Altogether, 90% of those operated on by 60 days of age are free of jaundice. The 10 year survival of those free of jaundice is 90%.[11] This would require paediatricians to see all infants who are jaundiced after 14 days of age and to investigate those who have jaundice associated with yellow (bile containing) urine for hepatobiliary disease (an incidence of about one in 500). Only one in 12–14 000 would have biliary atresia,[12] but the remainder would have disorders that are best managed if identified early. Infants should be seen for 'well baby' review not at 6 weeks of age but at 4 weeks as occurs in Japan.[13 14]

In this way, mild jaundice that had not caused concern to parents or primary health care advisers would come to the attention of doctors sufficiently early for biliary atresia to be identified by 8 weeks. The good results in Japan arise not because the cause of the disease is different there or solely because of earlier identification but also because cases are concentrated in units that have developed the necessary expertise.[13 14] In Britain only a minority of infants with biliary atresia are so privileged.[15]

I suspect that the Japanese are no better at making cars than other nations but are more organised.

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Erythema neonatorum toxicum

Toxic erythema of the newborn was originally described by Bartholomaeus Netlinger in 1472 and renamed erythema neonatorum toxicum by Leiner in 1912.[1] It is a benign self limited eruption that may be present at birth in up to 20% of cases,[2] although more typically it occurs 24 to 48 hours after birth.[3] Roughly 30–70% of newborn infants are affected. There is no racial or sexual predilection but there is increased frequency of erythema toxicum in infants with increasing birth weight and gestational age.[4]

Clinically, the lesions are firm, 1–3 mm, pale yellow or white papules and/or pustules on a red and swollen base. The resultant picture is that of a 'flea bite'. Atypically, the lesions may occur as single red macules, confluent macules, or irregular splotchy erythema up to 3 cm in size. There is a predilection for the lesions to occupy the anterior and posterior trunk but lesions may readily be found on the upper arms, thighs, and face. The palms and soles are almost never involved. Erythema toxicum usually lasts about five to seven days as crops of new lesions that heal without residual pigmentation. The eruption does not usually recur, though several questionable episodes have been documented within the month. No systemic involvement has been noted, though serum eosinophilia is seen in 7–18% of cases and tends to correlate positively with severity of the disease.[5] A diagnosis can be made routinely by preparation of a Tzanck smear, Giemsa stain, or Wright stain preparation of a pustule, which will show numerous eosinophils. (The Tsanck smear consists of removing the blister roof and preparing a slide from the scrapings of the base of the blister using a scalpel blade.) Histologically, the pustules are most often located in the epidermis just beneath the stratum corneum and are filled with eosinophils. Histological examination of a macule usually shows a perivascular infiltrate composed primarily of eosinophils and a few polymorphonuclear leucocytes and mononuclear cells.

The aetiology of erythema toxicum remains a mystery, though several hypotheses have been put forth. Keitel *et al* considered the atopic diathesis as an antecedent cause but found that the incidence of atopy in the families of affected infants was not greater than that in the general population.[4] The possibility that erythema toxicum was the result of an immediate hypersensitivity reaction to an allergen has been entertained, but no specific antigens or antibodies have ever been implicated.[2] A superficially more plausible hypothesis is concerned with the fragility of newborn skin. As erythema may readily be induced in newborn skin with light pressure and vesiculation by brief rubbing it might be suspected that erythema toxicum may be related to mechanical or thermal stimulation.[4] This hypothesis, however, does not explain why all newborns do not have erythema nor does it take into account the greater fragility of premature skin and the propensity of erythema toxicum to await full gestation before presenting itself as a problem to the infant. The production of eosinophilic pustules may be related more to a peculiar reaction of the skin of predisposed individual's experience than to a specific cause. If erythema toxicum is a reaction pattern of the skin we have yet to understand how to separate this particularly predisposed subpopulation. The aetiology of erythema toxicum is still unknown at present and there is no treatment needed because eruption resolves spontaneously and it has no known serious complications.

Differential diagnoses

Transient neonatal pustular melanosis. Transient neonatal pustular melanosis is more often present at birth than erythema toxicum and occurs more often in mature black neonates of both sexes.[6] There is no sexual preference for the disorder. Erythema toxicum and transient neonatal pustular melanosis can be seen together in the same infant and the lesions of each disorder readily separated morphologically. Transient neonatal pustular melanosis initially starts as very superficial vesiculopustular lesions. When the lesions decompress or burst they leave pigmented macules with a surrounding collerette scale. The lesions are most often present under the chin, on the forehead, the nape, the lower back, and occasionally the trunk, extremities, the cheeks.[7] Absent is the 'flea bitten' appearance of erythema toxicum, representing the peripustular oedema. The eruption may last several weeks to a few months. Histologically, the vesiculopustule is usually located beneath the stratum corneum and is filled with polymorphonuclear leucocytes or eosinophils, or both. Presence at birth, different clinical presentation, and a typical histologic picture help, therefore, to differentiate the two diseases.

Eosinophilic pustular folliculitis. Eosinophilic pustular folliculitis was originally described by Ofuji.[8] It is characterised by recurrent crops of follicular papulopustules located on the face, trunk, and extremities. Histologically, an intense infiltration of the hair follicle with eosinophils is seen. Lucky *et al* have recently described a number of such patients, one of whom was a newborn who was thought to have severe erythema toxicum.[9] The recurrent nature of the disorder, its predilection for the scalp, and associated peripheral eosinphilia noted during the attacks helped, however, to differentiate the two diseases.

Incontinentia pigmenti. Incontinentia pigmenti (Bloch-Sulzberger disease) is an X linked, dominantly inherited disease characterised by three dermatological stages. Initially, linear vesicular lesions that are usually present at birth evolve into verrucous lesions within weeks and are then followed by a peculiar swirled hyperpigmentation that may last for years. The vesicular and keratotic stages may each last from months to years. They are most often located on the trunk and extremities. Multisystem involvement is common with evidence of neurological, skeletal, ocular, and dental abnormalities occurring as the patient ages.[10] Histologically, a biopsy specimen of a vesicule would show a subcorneal or intraepidermal pustule filled with eosinophils. The histology is identical to erythema toxicum but the persistence of the eruption, the evaluation through different stages, and multiple system involvement help to differentiate the two diseases.

Infantile acropustolosis. Infantile acropustolosis was originally described by Kahn[11] and by Jarratt[12] and is characterised by recurrent crops of 1–2 mm intensely pruritic vesiculopustules found previously on the distal extremities of infants. It is more common in black infants and is predominantly found between the ages of 2 and 10 months. Several reports exist of onset in the neonatal period.[13] Histologically, subcorneal or intraepidermal pustules that are filled with polymorphonuclear and eosinophilic leucocytes and a sparse perivascular infiltrate may be found. Several cases with eosinophil filled pustules have been noted.[14] The characteristic distribution, recurrent nature, and predominant polymorphonuclear cell component in the pustules, however, set this order apart from erythema toxicum.

Other disorders. Several other diseases bear mention in this discussion of neonatal vesiculopustular eruptions. Miliaria is an extremely common eruption in the neonate secondary to sweat retention and is characterised by a vesicular eruption with subsequent maceration and obstruction of the exocrine ducts. The lesions are most often seen in the intertriginous areas, particularly the neck and axillae. Vesiculopustular eruptions of infectious aetiology, such as herpes simplex, varicella, or cytomegalovirus, must also be ruled out with a Tzanck smear preparation and culture, impetigo with routine Gram stain and culture, candidiasis with routine potassium hydroxide preparation and culture, and scabies with appropriate mineral oil preparations. Letterer-Siwe disease is characterised by the presence of purpura mixed among the eczematous papules, which contain the atypical histiocytes characteristic of this disorder.

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Original articles

Cytomegalovirus infection in day nurseries

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SUMMARY One hundred and seventeen children and 41 teachers in day nurseries were screened for cytomegalovirus (CMV) viruria over a period of one year. Thirty two (27%) children and two (5%) teachers were found to be excreting virus on at least one occasion. Restriction endonuclease typing showed that virus strains isolated from the children were dissimilar, with the exception of those from sibling pairs and one unrelated pair. The virus isolate from one teacher matched those from two unrelated children, while the isolate from another teacher could not be distinguished from that from a sibling pair. The CMV serological state of the 41 teachers was not significantly different from 500 matched controls and no seroconversions occurred.

It is concluded that although transmission of CMV among children and teachers may occur in day nurseries, the dissimilarity of most of the virus strains indicates that infection predominantly occurs outside. Furthermore, teachers in day nurseries showed no evidence of an increased risk of past CMV infection when compared with matched controls.

Cytomegalovirus (CMV) infection acquired during pregnancy may cause fetal damage,[1] but when infection occurs postnatally the clinical consequences are usually trivial.[2] In the United Kingdom 3–4 per 1000 children are born with congenital CMV infection[3] and a further 20% become infected during the first year of life.[2] The major source of early acquired infection is maternal breast milk.[4]

A non-maternal source of CMV infection thought to be important in the acquisition of CMV is group child care. In countries where most young children receive group care the rates of CMV infection are high in young age groups[2] and several studies of children attending day care centres have reported high rates of CMV excretion.[5-9] With the exception of two studies,[10 11] however, characterisation of CMV using deoxyribonucleic acid (DNA) restriction endonuclease analysis to show differences or similarities between virus isolates was not carried out, and without virus typing it can only be inferred that the reported high rates of excretion were due to transmission occurring within the centres. No studies have been performed in the UK. We report here the application of virus typing to CMV virus isolates obtained from children and teachers in day nurseries in south east England.

Methods

CMV excretion was studied in five day nurseries; three were ordinary local health authority day nurseries, primarily serving local and disadvantaged children, and two specialised in the care of physically, emotionally, or intellectually handicapped children. In each centre children spent the entire day at the nursery. Classes were selected at random in three nurseries. One class in the fourth nursery was selected because a child with congenital CMV infection and known to be excreting the virus was enrolled. In the fifth, another nursery with a child with congenital CMV infection, all children participated in the study. Within each class children played together, shared toys, and ate lunch in a common room.

Informed consent was obtained from the parents of the study children. Parents also completed a questionnaire that provided data on demographic variables and day nursery experience. In four nurseries urine samples were collected from the children every three months for one year. In the remaining nursery two collections were made six months apart.

Urine specimens were collected using sterile U bags if the child was not toilet trained, and those children who were toilet trained voided into a sterile container or a clean receptacle. Specimens were refrigerated at 4°C until inoculation on to monolayers of human embryonic lung fibroblasts. All tissue cultures were incubated and maintained for four weeks.

Informed consent was also obtained from the teachers in the day nurseries and urine samples were collected on the same schedule as for the children. In addition, blood samples obtained from the staff at the beginning of the study and then at six monthly intervals were tested for the presence of CMV complement fixing antibodies. Serial samples on the same individual were tested simultaneously.

Restriction endonuclease analysis was carried out on all isolates in which there was sufficient growth to allow typing. The method for CMV differentiation by restriction enzyme nuclease analysis developed by Huang *et al*[12] and modified and simplified by Garrett and Warren[13] was used. A minimum of three enzymes was used to cleave the 32P DNA prepared from each isolate, and the results of the typing were read blind.

The χ^2 test was used to test differences in sample proportions. When it was necessary to control for confounding variables the Mantel-Haenszel method for estimating odds ratio was used.[14]

Results

One hundred and seventeen children from the five day nurseries were included in the study. Characteristics of the study group are shown in Table 1. All the handicapped children were enrolled at the two special nurseries, which had significantly more white children than the others; 88% of the handicapped children were white compared with 38% of children in the other nurseries ($\chi^2=29{\cdot}05$, $p<0{\cdot}001$).

Overall, 32 (27%) children were found to be excreting CMV at some time during the study. Several characteristics were associated with increased risk of shedding virus (Table 2): significantly fewer white, older, and handicapped children were excreting CMV than other children.

Only one child attending a special nursery was excreting CMV. This child had congenital CMV and had been in the nursery for nine months before the first screen. No other child in his class of 25 children was found to be shedding CMV at either of the two screenings six months apart. In the other nursery for handicapped children no children were found to be excreting CMV during the study.

Table 1 *Characteristics of children studied (n=117)*

	No	*(%)*
Handicapped	41	(35)
Non-white	54	(47)
Sex:		
Male	59	(50)
Female	58	(50)
Age (years):		
<2	26	(22)
≥2	79	(78)
Parents' social class:		
Non-manual	24	(21)
Manual	39	(33)
Unemployed	25	(21)
Unknown	29	(25)
Toilet trained	69	(59)

Table 2 *Characteristics of children excreting cytomegalovirus*

	No (%) of children excreting cytomegalovirus (n=32)	*p Value*
Race:		
White	10 (16)	<0·01
Non-white	22 (40)	
Sex:		
Male	13 (22)	NS
Female	19 (33)	
Age (years):		
<2	12 (46)	<0·05
≥2	20 (25)	
Parents' social class:		
Non-manual	3 (15)	NS
Manual	11 (28)	
Unemployed	9 (36)	
Unknown	9 (31)	
Type of nursery:		
Special day nursery	1 (2)	<0·0001
Day nursery	31 (40)	

NS=Not significant.

In the remaining three day nurseries (A, B, and C) the prevalence of CMV excretion was high and 40% of children were found to be excreting CMV on at least one occasion. In nursery A the rate was 32% (9/28), in nursery B 46% (10/22), and in nursery C 50% (13/26). The number of children actually excreting virus at any one time ranged from 18% in nursery A to 37% in nursery C. Children excreting CMV tended to do so consistently throughout the study; 19% of the children excreting CMV did so for at least one year.

Neither the average age at which the child had entered the nursery nor the average time the child had been there was associated with excretion of the virus. Children excreting CMV entered the nursery at an average age of 16·5 months and had been in the nursery for an average of 15·5 months at the time of the first screen compared with 16·8 months and 16·2 months, respectively, for children who never excreted CMV.

Twenty (62%) of the 32 isolates were typed using restriction endonuclease techniques. The 12 isolates not typed were either lost due to technical problems or failed to yield sufficient growth for typing. Examples of similar and different oligonucleotide patterns have been described previously.[15] In nursery A nine children were excreting CMV at some time during the study. Isolates from six children were typed and two, from siblings, were found to have indistinguishable DNA patterns. Ten children were excreting CMV at some time in nursery B and isolates from nine were typed. Again two siblings excreted virus with indistinguishable oligonucleotide patterns as did two unrelated children. All the isolates were dissimilar to that obtained from the child with congenital CMV. In nursery C it was only possible to type isolates from five of the 13 children excreting CMV, of which three were dissimilar and those from two siblings could not be distinguished. Overall, therefore, two unrelated children attending the same nursery and three sibling pairs shed virus that could not be distinguished.

Forty one teachers were employed in the five day nurseries. Their ages ranged from 19 to 57 years, with a mean of 32·4. Eighty eight per cent were white. To determine whether the teachers were at increased risk of acquiring CMV, the prevalence of CMV antibody state in the teachers was compared with that of 500 women in their first pregnancy, matched for race and social class, attending a maternity unit in the same area. As the mean (SD) age of the teachers (32·4 (11·9) years) was significantly higher than that of the controls (29·53 (4·46) years) ($t=3·29$, $p<0·001$) the Mantel-Haenszel method was used to determine whether there was a significant difference in CMV antibody state between the groups. CMV seropositivity was found in 66% of the teachers compared with 53% of the controls. The adjusted odds ratio (1·67) for these two rates was not significant ($\chi^2=1·47$, 95% confidence limits 0·739–3·6).

None of the 14 seronegative teachers seroconverted during the study, but two teachers, both from the same nursery, did excrete virus. The oligonucleotide patterns of virus isolates obtained from both teachers were compared with each other and with those from children in the nursery. The DNA patterns of isolates from the two teachers were dissimilar. The pattern of the isolate from one of the teachers could not be distinguished, however, from the DNA pattern of isolates from a sibling pair. The other teacher excreted virus that could not be distinguished from that isolated from another child in the nursery. As the teachers were both seropositive at the beginning of the study the direction of transmission—child to teacher or teacher to child—could not be determined.

Discussion

The present study confirms previous reports of a high prevalence of CMV excretion in young children attending day nurseries.[6-9] The application of restriction enzyme typing of viral DNA allows transmission pathways to be identified with more precision, although in the present study a substantial proportion of the virus strains could not be typed owing to difficulties in growing sufficient quantities of the virus. The dissimilarity between strains from all but two children other than siblings suggests that most children acquired their infection outside the nursery. Although virus strains were not dissimilar in two unrelated children, suggesting horizontal transmission of infection, this may reflect an extraordinary chance event. In a parallel family study in which an infant acquired infection after a blood transfusion[15] a strain indistinguishable from those isolated from the above two nursery children was identified; epidemiological investigation failed to identify any common source.

Two previous studies in day nurseries have used the restriction enzyme technique, but no teachers were included.[10 11] Adler studied one nursery of 66 children where 16 were excreting CMV.[10] Seven children under 29 months were excreting CMV strains that had indistinguishable DNA patterns. Four other children were excreting a virus different from the first group but indistinguishable from each other. Two day care centres were studied in Sweden.[11] In one, seven of 20 children were excreting CMV, three had indistinguishable DNA patterns, and four were unique. In the other nursery five of 16 children were excreting CMV and all stains were unique.

In a largely white middle class population in west London as many as 20% of children acquired CMV by the age of 1 year and continued to shed virus for up to three years. (Peckham C. Unpublished observations.) One third of the children whose mothers were seropositive, however, were excreting CMV by their first birthday. Forty per cent of the children in our day nursery study were non-white, a population known to have a higher seropositive rate. Many of the children would probably have been excreting virus, therefore, after infection acquired from their mothers and before entering the day nursery.

Data from previous day care studies in the United States suggest that virus transmission between children may occur within day centres. In one study 51% of children were excreting CMV, with the highest rate in children under 24 months (83%);[6] at least 12% of these children had seronegative mothers. In another study rates of CMV excretion were significantly higher for children receiving day care compared with children staying at home.[7] Only 8% of the children at home had viruria compared with 57% of children in day care, but without restriction enzyme analysis it is not possible to draw any firm conclusions. Two case reports have described situations where transmission of CMV was assumed to have occurred but when restriction endonuclease typing was carried out this was found not to have been the case.[16 17]

Our study points to the risk of generalising from only one or two nurseries. The wide variation in the rates of CMV excretion (0% to 36%) in our nurseries indicates that not all day care settings are the same. We were asked to include two nurseries in the study because two children known to have congenital infection were considered to be a potential source of infection for other children and staff. In both situations there was no evidence that this was the case and in the nursery for handicapped children no other child was found to be shedding CMV.

The risk of CMV infection for teachers in day care centres cannot be established from our data as numbers are too small. Although in two cases we were unable to distinguish virus isolates from children and teachers, the seropositivity rate for teachers was not significantly different from controls and no seroconversion occurred. Further prospective studies are required to determine whether the risk of infection among day nursery teachers is different from that of women of similar age and background in the general population.

Although the findings suggest that transmission of infection may occcur within some nurseries, this does not seem to be the case for most infections. CMV infection is commonly acquired in the first year of life, particularly among infants of seropositive mothers, and virus shedding persists for a prolonged period. It is not surprising, therefore, that virus excretion is common among young children attending day nurseries. In view of the fact that virus shedding was more prevalent in the younger than the older children and was not related to the age at which the children entered the nursery nor to the duration they had been there and the dissimilarity of most of the virus isolates, the present study indicates that most infection probably occurred before entering the nursery.

Dr David Nelson carried out this work in 1983 as a Millbank Scholar.

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Prediction and management of nocturnal hypoglycaemia in diabetes

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SUMMARY Blood glucose measurements were made at 2200, 0200, and 0800h in 102 children with diabetes during a 24 hour planned admission to hospital. Nocturnal hypoglycaemia (<3·0 mmol/l) occurred in 24 of 71 (34%) children on twice daily insulin and in three of 31 (10%) children on once daily insulin. Predictive value modelling showed that a blood glucose concentration of less than 7 mmol/l at 2200h was the best predictor of nocturnal hypoglycaemia, with a sensitivity of 63%, specificity of 94%, and positive and negative predictive values of 83%. Blood glucose measurement at 0800h had no predictive value for nocturnal hypoglycaemia. The mean (SD) glycosylated haemoglobin concentration of children on twice daily insulin who had nocturnal hypoglycaemia was 55 (8) mmol HMF/mol Hb, which was significantly less than that of children on twice daily insulin who did not have hypoglycaemia (64 (11) mmol HMF/mol Hb) or those on once daily insulin (62 (11) mmol HMF/mol Hb). A controlled trial was then performed in which 29 children with diabetes who had a blood glucose concentration at 2200h of <7 mmol/l measured by Reflocheck were randomised into two groups, one of which received 10 g carbohydrate supplement and the other of which did not. Thirteen of the 14 children in the control group had hypoglycaemia at 0200h, whereas the snack prevented hypoglycaemia in 12 of 15 in the test group. Blood glucose values in the two groups at 0800h were similar. We conclude that bedtime glucose measurement in children on twice daily insulin is a useful predictor for nocturnal hypoglycaemia, which can be prevented by a small carbohydrate snack in those at risk.

Unrecognised nocturnal hypoglycaemia may be a widespread and important problem in children with diabetes and is certainly a phenomenon that is difficult to detect. Failure to recognise nocturnal hypoglycaemia in adults has been reported to lead to transient hemiparesis,[1] organic personality syndrome,[2] and a syndrome masquerading as senile dementia.[3] Attempts to identify individuals at risk have included the measurement of early morning blood glucose concentrations[4] or overnight urinary cortisol concentrations.[5] Recently, Pramming *et al* reported that nocturnal hypoglycaemia may be predicted with reasonable accuracy in adults with diabetes by the measurement of an evening blood glucose concentration at 2300h.[6]

Nocturnal hypoglycaemia in children with diabetes has been studied, but less than in adults.[7-9] A frequency of 10–19% has been reported in children treated with twice daily insulin,[8 9] and it has been claimed that one consequence of unrecognised nocturnal hypoglycaemia has been overtreatment with insulin.[7] The present study assessed the prevalence of nocturnal hypoglycaemia in a sample of children with diabetes and tested the value of bedtime blood glucose measurements as a predictor of nocturnal hypoglycaemia in children who eat and go to bed earlier than adults and who were treated with insulin once or twice daily. The effect of a small bedtime carbohydrate snack in preventing hypoglycaemia in those at risk was then evaluated in a controlled trial.

Patients and methods

Patients. There were two phases: (1) the prevalence and prediction study, which took place from January 1983 to January 1984, and (2) the intervention study, which took place from January to August 1984. The subjects were children admitted to hospital for annual review of their diabetic control.

Conversion: for HbA_{1c} by electrophoresis, 1 mmol HMF/mol Hb=0·19%; for HbA_{1c} by column chromatography, 1 mmol HMF/mol Hb=0·21%.

They were aged 3 to 16 years and all had had diabetes for more than one year. No child had symptoms of nocturnal hypoglycaemia and all were clinically well when admitted between 1000 and 1300h for a 24 hour stay in hospital. The admission helped to standardise the times of insulin injection and food intake and the amount of exercise taken. Carbohydrate intake followed the recommendations of the British Diabetic Association, with about 50% being rich in polysaccharides. The last food intake was 90 minutes before the bedtime blood sample was taken, which was collected at about 2200h. Further samples were collected at 0200h and 0800h. No child woke at 0200h due to blood sampling. Some children were studied in each phase.

Prevalence and prediction study

There were 102 children in the prevalence and prediction study. Seventy one were receiving twice daily insulin mixtures: 32 took Monotard/Actrapid (Novo) and 39 took Humulin Isophane/Soluble (Lilly). The daily total insulin dose was similar in the two groups, being 0·62–2·50 U/kg (mean 1·01 U/kg) and 0·40–1·54 U/kg (mean 0·93 U/kg), respectively. Thirty one took a long acting insulin or an insulin mixture once daily in a dose ranging from 0·25 to 1·35 U/kg (mean 0·90 U/kg).

Intervention study

There were 97 children in the intervention study. Twenty nine (30%) had a blood glucose concentration of <7·0 mmol/l at 2200h measured by Reflocheck (Boeringer, Mannheim). They were randomised into two groups: (1) the control group (10 boys and four girls), which received no carbohydrate supplement, and (2) the test group (nine boys and six girls), which received 10 g carbohydrate as soon as the low bedtime blood glucose result was known. Twenty one children received twice daily insulin and eight received single dose treatment in the morning. All children in both studies had a 20 g carbohydrate snack at 2015h and those on twice daily insulin had their evening dose 20 minutes before the main meal at 1715h.

Methods. Fingertip heparinised blood samples were taken from all children at 2200, 0200, and 0800h and stored at 4°C until analysed for glucose by the hexokinase method[10] later in the day. In the intervention study blood glucose concentration was also measured at the bedside by Reflocheck (Boeringer, Mannheim).

Glycosylated haemoglobin (HbA_{1c}) (normal range 29–39 mmol HMF/mol Hb) was measured in all children during admission by a colorimetric assay,[11] and mean HbA_{1c} concentrations in different groups were compared by Student's unpaired *t* test. For the purpose of this study nocturnal hypoglycaemia was defined as a blood glucose concentration of less than 3 mmol/l.

Results were analysed using the predictive value model,[12] employing the following definitions.

(1) Sensitivity: the proportion of children with nocturnal hypoglycaemia at 0200h with a blood glucose concentration less than a given value at 2200h.

(2) Specificity: the proportion of children without nocturnal hypoglycaemia at 0200h with a blood glucose concentration greater than a given value at 2200h.

(3) Positive predictive value: the proportion of children with a blood glucose concentration less than a given value at 2200h who also had nocturnal hypoglycaemia at 0200h.

(4) Negative predictive value: the proportion of children with a blood glucose concentration greater than a given value at 2200h who did not have nocturnal hypoglycaemia at 0200h.

Results

Prevalence and prediction study.

Twice daily insulin

The blood glucose concentration fell to less than 3·0 mmol/l at 0200h in 24 of the 71 children (34%). Ten of the children with hypoglycaemia had received Monotard/Actrapid mixtures and 14 had received Humulin Isophane/Soluble mixtures.

The positive predictive values of blood glucose concentrations of less than 5, 6, 7, 8, 9, and 10 mmol/l at 2200h for nocturnal hypoglycaemia at 0200h are shown in Table 1, from which it can be seen that the best predictor was a blood glucose concentration of less than 7 mmol/l at 2200h, which had both a positive and a negative predictive value of 83%, a sensitivity of 63%, and specificity of 94%. More explicitly, 18 children had a blood glucose concentration less than 7 mmol/l at 2200h, and of

Table 1 *Predictive value models for nocturnal hypoglycaemia at 0200h from different blood glucose concentrations at 2200h*

Blood glucose (mmol/l) at 2200h	*Sensitivity*	*Specificity*	*Predictive value*	
			Positive	*Negative*
<5	42	96	83	76
<6	54	94	81	80
<7	63	94	83	83
<8	75	81	69	87
<9	83	81	71	91
<10	92	74	65	95

these, 15 had a concentration of less than 3 mmol/l at 0200h. Fifty three children had a blood glucose concentration of more than 7 mmol/l at 2200h, and of these, nine had a concentration of less than 3 mmol/l at 0200h. The relation between the blood glucose concentration at 2200h and the change in blood glucose from 2200h to 0200h is shown in the Figure. In eight of the 24 children with nocturnal hypoglycaemia the blood glucose concentration at 0200h was less than 2 mmol/l. The mean (SD) blood glucose concentration at 0800h of the children who had nocturnal hypoglycaemia was significantly lower (10·0 (6·9) mmol/l) than that of those who had not (13·6 (5·9) mmol/l). Similarly, the mean (SD) HbA_{1c} concentration of the children with nocturnal hypoglycaemia was significantly less than that of those with no nocturnal hypoglycaemia (55 (8) *v* 64 (11) mmol HMF/mol Hb). The predictive value of blood glucose measurements at 0800h for nocturnal hypoglycaemia the previous night was no better than chance (results not shown).

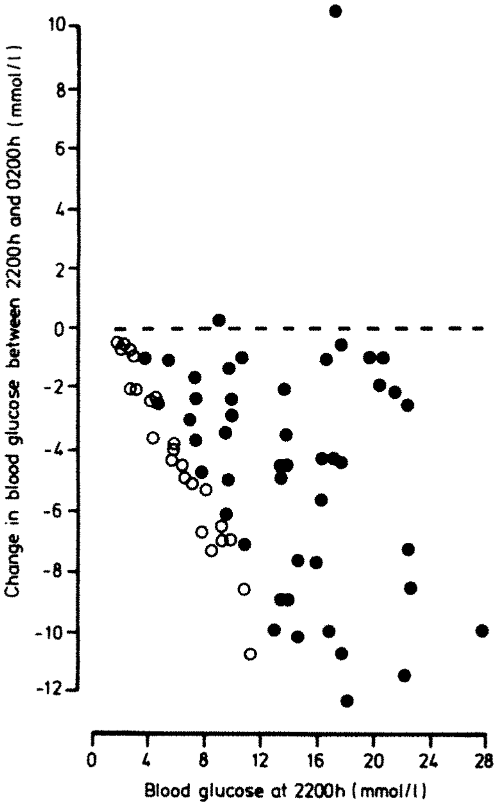

Figure *Blood glucose concentration at 2200h correlated with change in blood glucose between 2200h and 0200h in 71 children with diabetes taking twice daily insulin. Children with blood glucose concentrations of more than 3·0 mmol/l at 0200h are shown by solid circles and those with concentrations of less than 3·0 mmol/l at 0200h by open circles.*

Once daily insulin

Three of the 31 children who received once daily insulin developed nocturnal hypoglycaemia. The number was too small for comparison with those receiving twice daily insulin. The mean (SD) HbA_{1c} concentration of the 28 children who did not have nocturnal hypoglycaemia was 62 (11) mmol HMF/mol Hb, which was very similar to that of the 47 children on twice daily insulin who did not have nocturnal hypoglycaemia.

Glycosylated haemoglobin

There was no correlation between the blood glucose concentration at 0200h and the HbA_{1c} concentration in any subgroup or in the total study sample.

Intervention study. In all cases the laboratory measurement of blood glucose confirmed the Reflocheck estimate at 0200h of <7 mmol/l. The mean (range) of the laboratory determinations was 3·8 (1·6 to 6·0) mmol/l. Results were analysed, taking account of whether the children had insulin once or twice a day (Table 2).

Twice daily insulin

Ten of the 11 children in the control group had hypoglycaemia at 0200h, whereas only two of the 10 in the test group had a blood glucose concentration of <3·0 mmol/l at 0200h. The blood glucose concentration fell between 2200 and 0200h in every child in the control group, whereas the concentration rose in eight of the children in the test group, but one of these had hypoglycaemia at 0200h notwithstanding. By 0800h a similar mean rise in

Table 2 *Blood glucose concentrations at 2200h and change in blood glucose at 0200h and 0800h in children with diabetes at risk of nocturnal hypoglycaemia. Values are mean (SEM)*

Patient group	*(n=)*	*Blood glucose or change in blood glucose (mmol/l)*		
		2200h	*0200h*	*0800h*
Twice daily insulin				
Bedtime carbohydrate	(10)	3·2 (0·4)	+0·9 (0·4)	+7·9 (1·4)
No carbohydrate	(11)	4·0 (0·5)	−2·0 (0·4)**	+7·6 (2·6)
Once daily insulin				
Bedtime carbohydrate	(5)	3·8 (0·2)	+2·1 (1·3)	+3·5 (1·8)
No carbohydrate	(3)	4·8 (0·8)	−1·9 (0·6)*	+5·7 (0·7)
All patients				
Bedtime carbohydrate	(15)	3·4 (0·3)	+1·3 (0·5)	+6·3 (1·2)
No carbohydrate	(14)	4·2 (0·4)	−2·0 (0·3)**	+7·1 (1·9)

*p<0·05, **p<0·01 by Student's *t* test.

blood glucose concentration of 7–8 mmol/l had occurred in both groups, but the range of change was greater in the control patients, suggesting that a Somogyi effect might have occurred in some.

Once daily insulin
There were fewer patients taking insulin once daily, reflecting current clinical practice. There had been a fall in blood glucose concentration at 0200h in all three of the control patients, and two became asymptomatically hypoglycaemic. In all five test patients the blood glucose concentration had risen at 0200h. The mean rise in blood glucose concentration at 0800h in both groups was similar but less than that seen in patients taking twice daily insulin.

Glycosylated haemoglobin
The quality of diabetic control as reflected in the HbA_{1c} measurements ranged from 39 to 60 mmol HMF/mol Hb but was similar in all four subgroups, mean (SD) values (in mmol HMF/mol Hb) being 53 (6) in test patients on twice daily insulin, 47 (5) in control patients on twice daily insulin, 55 (3) in test patients on once daily insulin, and 52 (9) in control patients on once daily insulin.

Discussion

This project was designed to measure the prevalence of nocturnal hypoglycaemia in children with diabetes with minimum inconvenience under relatively standardised conditions, which were thought to favour hyperglycaemia rather than hypoglycaemia because of the relative inactivity associated with admission to hospital. A blood glucose concentration of 3 mmol/l was used as a working definition of hypoglycaemia based on previous work and 0200h was chosen as the sampling time because of the authors' previous experience in diabetic summer camps where most symptomatic hypoglycaemia occurred between 0100 and 0300h.

About one third of the children taking insulin twice daily experienced symptomatic nocturnal hypoglycaemia, and among these one third had severe hypoglycaemia with a blood glucose concentration of less than 2 mmol/l. In contrast, only one tenth of the children receiving insulin once a day experienced nocturnal hypoglycaemia. If the three subgroups, twice daily insulin with or without hypoglycaemia and once daily insulin without hypoglycaemia, were considered the quality of diabetic control judged by HbA_{1c} concentrations was indifferent to poor and was similar in the two subgroups without hypoglycaemia, whereas the patients experiencing hypoglycaemia had a significantly lower mean HbA_{1c} concentration, although there was no direct correlation between HbA_{1c} and blood glucose concentrations at 0200h within this subgroup. This is not surprising as the HbA_{1c} reflects long term overall glucose homeostasis and the measurement of blood glucose at 0200h took place on one night only. A legitimate inference is that patients with lower HbA_{1c} concentrations taking insulin twice daily are more prone to nocturnal hypoglycaemia. Should this cause concern or be regarded merely as an epiphenomenon? In favour of the latter view is that the children were clinically well at the time of study and the hypoglycaemia, by definition, was asymptomatic. Against this is the evidence that nocturnal hypoglycaemia in adults can damage the brain, and it is plausible to suggest that the effect is more likely to be gradual and cumulative rather than abrupt. Anecdotally, two of the children in the present study subsequently had transient hemiparesis and a third had early morning convulsions, all as complications of nocturnal hypoglycaemia. All three children had HbA_{1c} concentrations below 50 mmol HMF/mol Hb at the time and were perceived to have excellent diabetic control.

While this study may have fuelled the debate on what is optimal control for a child with diabetes without providing a clear answer to that question, it has also clarified ways in which nocturnal hypoglycaemia may be predicted. Analysis of bedtime and early morning blood glucose concentrations has shown clearly that a bedtime concentration of less than 7 mmol/l is a useful predictor that hypoglycaemia will occur. This is in keeping with the observation of Pramming *et al* that 80% of adults on twice daily insulin with a blood glucose concentration of less than 6 mmol/l at 2300h had nocturnal hypoglycaemia.[6] We were unable to find any association between nocturnal hypoglycaemia and subsequent blood glucose concentrations measured at 0800h, which contrasts with an earlier report.[8]

The simple intervention study confirmed that bedtime glucose monitoring with the Reflocheck overestimated blood glucose concentrations in the low and low-normal glycaemic range[13] but was none the less useful in predicting which children would experience nocturnal hypoglycaemia. More importantly, we have shown that this risk can be ameliorated by a 10 g carbohydrate snack without prejudice to the overall quality of diabetic control as reflected in the 0800h blood glucose reading. We think that this simple procedure is worth recommending to families for use at home, in particular in those cases where there may be cause to suspect that nocturnal hypoglycaemia is occurring in the child with diabetes.

Ideally, each child should have been studied on more than one occasion and acted as a self control. We did not consider it justified to admit a child to hospital more than once and preferred to use a less elegant experimental model but one that was ethically more acceptable. Normal bedtime for the children in this study was from 2030 to 2200h, and the blood glucose testing and carbohydrate supplementation did not change this routine, but care was taken to ensure that those who had extra carbohydrate at 2200h cleaned their teeth.

We are grateful to the Chemical Pathology Service of the Children's Hospital and Royal Hallamshire Hospital for measuring blood glucose and glycosylated haemoglobin concentrations.

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Parental smoking, breast feeding, and respiratory infection in development of allergic diseases

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SUMMARY Environmental factors were examined as determinants of clinical disease in a five year prospective study of 73 children born to atopic parents. Clinical follow up for evidence of eczema and wheezing was combined with regular skin testing, immunoglobulin assay, and respiratory viral culture where appropriate.

Thirty six children developed eczema, which was often associated with a positive result of a skin test to ingestants in the first year and inhalants by the fifth year. Thirty two children developed one or more episodes of wheeze. Fifteen children wheezed once only, and not all of these developed atopy.

No pattern of respiratory infection in early life was characteristic of children with recurrent wheeze. There was a significant difference in parental smoking habits between children with and without episodes of wheeze at the fifth birthday. No protective effect of breast feeding could be shown.

The development of allergic disease in susceptible children is influenced by many environmental factors. Advice to families about reduction of environmental allergens continues to pose problems, but parents should be advised to avoid smoking in the child's presence.

The relation between the atopic state and the clinical expression of diseases such as bronchial asthma or atopic dermatitis remains unclear. Most young children with these disorders are atopic and exposure to allergen can, in sensitive individuals, induce bronchospasm and eczematous skin changes. Not all atopic subjects, however, develop disease. The possibility that additional influences are required for expression of disease to occur has received much attention. There have been reports on the role of diverse environmental factors in atopic subjects, including season of birth,[1] respiratory infections,[2] and state of breast feeding.[3–8]

In this five year prospective study we have followed a cohort of children (n=97) at risk of allergic disease, seeking the development of eczema, recurrent wheezing, and seasonal rhinitis. We have attempted to examine how environmental factors interact on the atopic constitution and produce symptoms of disease. The incidence of early respiratory infections and the development of specific antibody to common allergens in these children has previously been reported.[9 10]

Patients and methods

Study design. One hundred babies were selected for study before birth on the grounds that one parent gave a history of hay fever or asthma. This selection was designed to provide a cohort of children of whom about half would be expected to develop evidence of atopy, those without atopy acting as controls. In this study atopy was defined as the presence of eczema and/or one or more positive results of a cutaneous prick test to common allergens. Written consent from pregnant mothers was obtained after full explanation that the baby would be subjected to venepunctures and the passage of a soft nasal catheter during the course of the study. All the babies were born in the maternity department of a district general hospital. The mean birth weight on leaving hospital was 3280 g.

At one year there were 92 families on follow up. Most of the study families continued to live in the area served by the hospital, and 73 remained on follow up on the child's fifth birthday (Table 1). Parents were asked to keep a diary of their feeding

Table 1 *Reasons for the 27 withdrawals from the study*

Reason	*No*
Moved away	12
Lost to follow up	10
Parents decided not to continue	4
Other reason	1
Total	27

methods and smoking habits. The date of the first cow's milk feed was recorded, but this information was not available to the paediatrician (JJC) who examined the babies. The social class classification was recorded (Registrar General's Classification, 1971).

Clinical assessment. All babies were examined at birth, at 3, 6, and 12 months, and annually thereafter. At each hospital visit a clinical history was taken and added to by a daily record of respiratory symptoms and skin problems kept by the parents. Clinical examination of the skin and the respiratory tract was carried out at each visit. In addition, parents were asked to notify the hospital whenever respiratory symptoms developed; a clinical examination was then made, usually at home. A diagnosis of eczema was made when the skin of the face or flexures showed roughening, redness, or intense pruritus that persisted for four weeks or more. Transient spots or cradle cap were not regarded as eczema. The presence of eczema and wheezing was confirmed in all cases by the paediatrician (JJC) or general practitioner. Hay fever was regarded as present if nasal discharge occurred in at least two spring/summer seasons. In this report children are regarded as atopic if they developed eczema or had at least one positive result of a cutaneous prick test during the study.

Laboratory investigation. At each hospital visit immediate skin testing for hypersensitivity was carried out by prick testing with six common allergens—namely, *Dermatophagoides pteronyssimus* (house dust mite), mixed grass pollen, cat fur, dog dander, hen's egg, and cow's milk (Bencard Ltd). A control solution and a 1/1000 histamine solution were also used. The diameter of the wheal was recorded at 15 minutes; a positive reaction was recorded when a wheal was 3 mm greater than that of the negative control. All subjects showed reactivity to the histamine solution.

At each visit venepuncture was performed and the serum assayed for immunoglobulin concentrations, including total serum IgE.[11]

Direct viral culture was attempted whenever respiratory symptoms were notified. Nasopharyngeal secretions were taken from the symptomatic baby in the home and transported at 0°C to the laboratory. The methods of tissue culture have been described elsewhere.[9]

Saliva samples were collected from all children at 3 years. These samples were assayed for IgA, using a double antibody radioimmune assay.[12] This assay is specific for alpha determinants on IgA, is not inhibited by secretory piece, and is not influenced by the molecular weight of the IgA.

Statistical analysis was undertaken using analysis of variance, t test, and χ^2 test. As a result of skewness in the distribution of the IgE results, data were logarithmically transformed (log (1+x)) before significance tests were performed.

Results

Clinical disease. Of the 73 children who remained on follow up for five years, 36 developed eczema. In 34

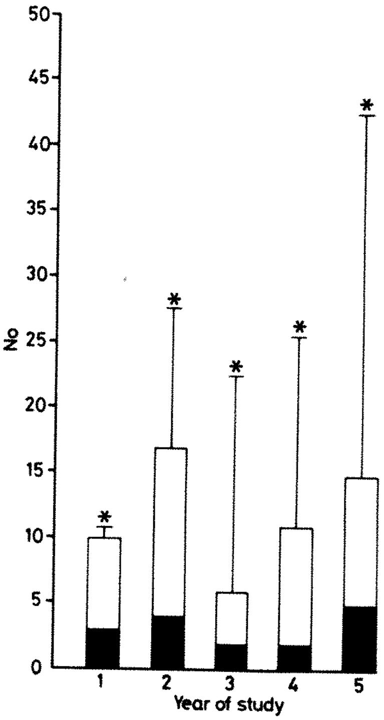

Fig. 1 *Incidence of wheezing by year of study. Total bars (white+black) show number of children who experienced episodes of wheeze in each year; black bars show number of these children who had eczema in each year. Asterisk denotes total number of episodes of wheeze in each year.*

(94%) of these the skin rash became apparent within the first two years of life. In most (n=31) the skin rash persisted for less than one year and did not present an important clinical problem. In five subjects persistent skin inflammation, requiring appropriate topical treatment, was present, but even in these children there was a tendency to improve with age.

Thirty two children (44%) had one or more episodes of wheezing. Most children (69%) had their first episode within the first two years of life. Fifteen children had a episode of wheeze on a single occasion only. Four of the 15 children who wheezed only once showed no evidence of atopy during the five year follow up. As the remainder (n=17) went on to develop recurrent attacks of wheezing the actual number of episodes of wheeze each year increased with age (Fig. 1). Eleven had four or more attacks in the five years and all of these received medical treatment, including admission to hospital in two cases. Fifteen of the 17 children with recurrent wheeze either developed eczema or had multiple positive results of cutaneous prick tests during the study.

Skin tests and clinical disease. The skin test reactivity to the six common allergens is shown in Figure 2. Responses to egg and milk were most prevalent in years one and two, after which they decreased, whereas those to the major inhalant allergens house dust mite and grass pollens were more prevalent in the later years of the study. Of the 36 children with a diagnosis of eczema, 21 were atopic on the basis of results of the skin test. Eleven of these showed egg sensitivity in the first year compared with only three of the 37 children without eczema ($p<0.05$). During the first year ingested allergens accounted for 86% of positive reactions in children with eczema (Table 2). By contrast, at year five, inhalant allergens accounted for 26 of 27 positive reactions in children with eczema.

Children with recurrent wheezing showed an increasing number of positive reactions to inhalant allergens as age increased, with 16 of 18 being classified as atopic on this basis at the end of the study. Of the 32 children who wheezed, 22 had at least one positive result of a prick test. No characteristic pattern of skin test responses occurred in children with wheeze to distinguish them from the atopic subjects who did not wheeze. Six of the eight patients with hay fever developed a positive skin reaction to mixed grass pollens within five years.

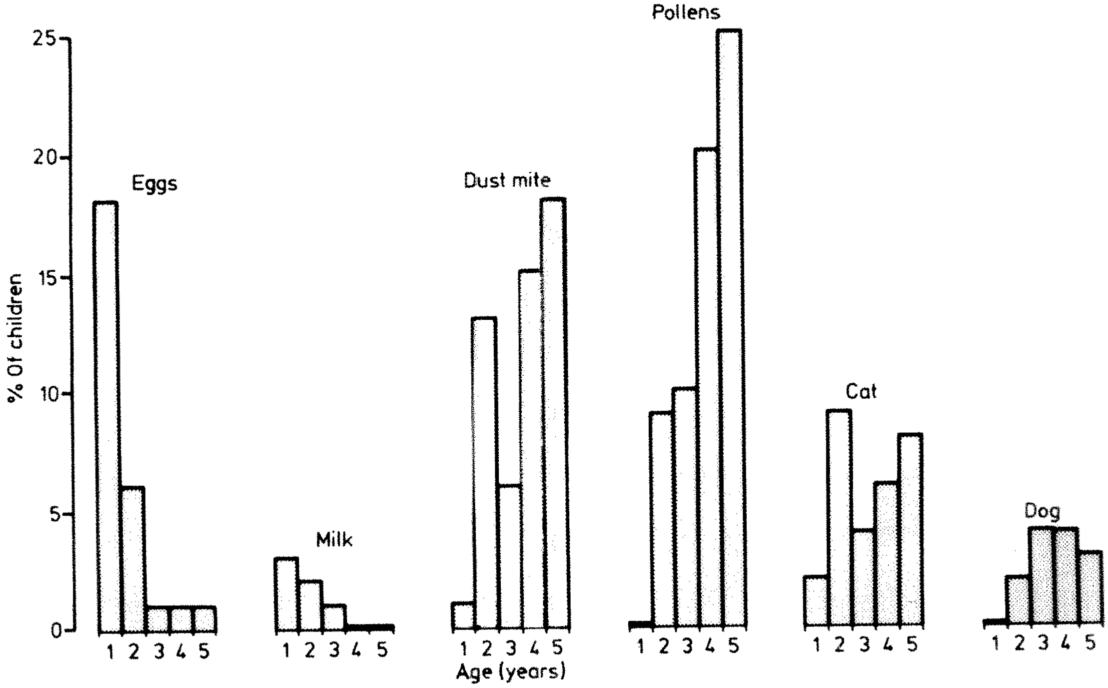

Fig. 2 *Percentage of children with positive results to skin tests for the six common allergens.*

Table 2 *Positive reactions to skin tests at 1, 2, 3, and 5 years in 36 children who developed eczema*

Age (years)	*Antigen*					
	Egg	*Dust mite*	*Pollens*	*Cat*	*Dog*	*Milk*
1	6	—	—	1	—	3
2	4	7	5	4	1	2
3	1	4	4	3	2	1
5	1	10	11	3	2	—

Immunoglobulin concentrations and clinical disease. Immunoglobulin E concentrations were significantly raised in both patients with eczema (Fig. 3) and those with recurrent wheezing (Fig. 4) when compared with those children who did not have these diseases at all ages after 3 months ($p<0\cdot05$). Children who wheezed only once had IgE concentrations that were not significantly different from those of children who did not wheeze at all ($p>0\cdot05$).

No differences in serum IgA concentrations were apparent at any age between 3 and 60 months between children with and without eczema. The salivary IgA values in 3 year old subjects were not significantly different in those with and without eczema, all being within the normal adult range.[6] There was no significant difference in serum IgA concentrations between those who did and did not have episodes of wheeze ($p<0\cdot05$).

Parental smoking. At the children's first birthday the number of those who had developed or were to develop wheezing was equally distributed between parents who did or did not smoke at that time. By 5 years, however, 62% of parents who smoked had children who had experienced episodes of wheeze compared with 37% in families where the parents did not smoke. The difference was significant ($p<\cdot05$) (Fig. 5).

When total serum IgE concentrations of children were compared between the families where the parents smoked and those where the parents did not smoke no significant difference could be found at any age ($p>0\cdot05$).

Respiratory infections. Successful isolations of virus became less common as the children grew up, probably due to sampling difficulties. In all subjects throughout the study respiratory viruses (rhinovirus, respiratory syncytial virus, and para-influenza virus) were isolated from children with both coryzal and wheezy syndromes. The 15 children who wheezed only once often had associated coryzal symptoms. In this group five positive respiratory viral isolates were made (three respiratory syncytial virus, two para-influenza virus).

Respiratory infections occurred more often in the atopic children (mean 20·7 over five years) than in the non-atopic children (mean 15·6), but this difference did not reach significance. There was a similar

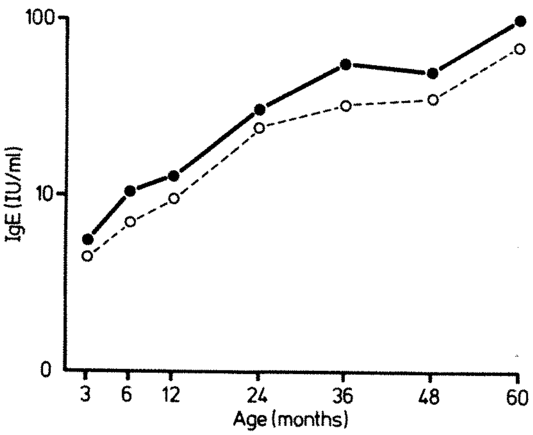

Fig. 3 *IgE concentration in children according to whether they developed eczema or not.* ●——● *= Those with eczema (n=36),* ○– – –○ *= those without eczema (n=37).*

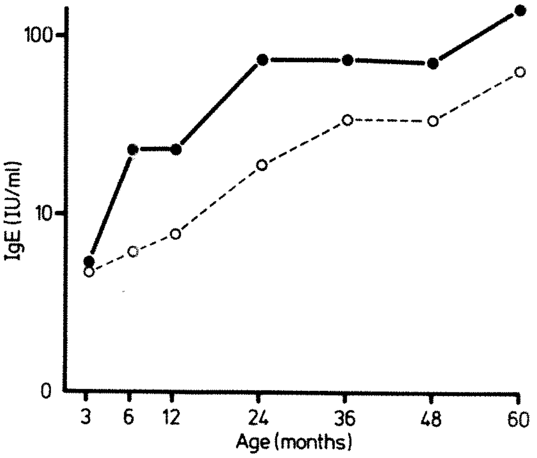

Fig. 4 *IgE concentration in children according to whether they had episodes of wheeze or not.* ●——● *= Those with recurrent wheeze;* ○– – –○ *= those without wheeze.*

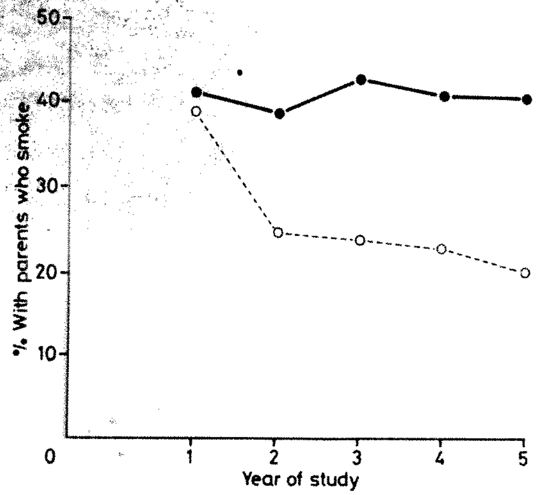

Fig. 5 *Parental smoking habits and wheezing in total study population.* ●——●=*Children with wheeze (n=32);* ○– – –○=*children without wheeze (n=41).*

pattern of respiratory virus infections in the atopic children during the first year of life compared with those who did not develop wheezing (Table 3).

Breast feeding. The duration of breast feeding was taken as the time from birth to the introduction of the first cow's milk or cow's milk formula feed.

In all, 55% of children received no cow's milk during the first four weeks of life and 12% were totally breast fed for over three months.

There was no evidence of any relation between the duration of breast feeding and the incidence of eczema or positive skin tests ($p>0{\cdot}05$) (Table 4).

No protective effect of breast feeding against asthma could be shown.

Atopic children and environmental factors. Forty eight children were identified as atopic. Twenty two developed episodes of wheeze and 26 did not. As the genetic predisposition to atopy was similar the two subgroups were compared for environmental influences.

No significant differences between the groups could be shown for social class, season of birth, or duration of breast feeding. The atopic children who had episodes of wheeze did not have significantly more respiratory infections, and the virus isolates in the first year were similar in both groups (Table 3).

There were significantly more parents who smoked cigarettes among the families of atopic children who had episodes of wheeze at 5 years of age than in the families of children who did not have episodes of wheeze ($p<0{\cdot}05$) (Fig. 6).

Discussion

The prediction that roughly half of these children

Table 4 *Duration of breast feeding according to atopic state*

Atopic state	*Duration of breast feeding (weeks)*			
	>4	*5–13*	*14+*	*Total*
None	14	10	1	25
Skin test positive only	4	7	1	12
Eczema only	7	6	2	15
Skin test positive and eczema	8	8	5	21
Total	33	31	9	73

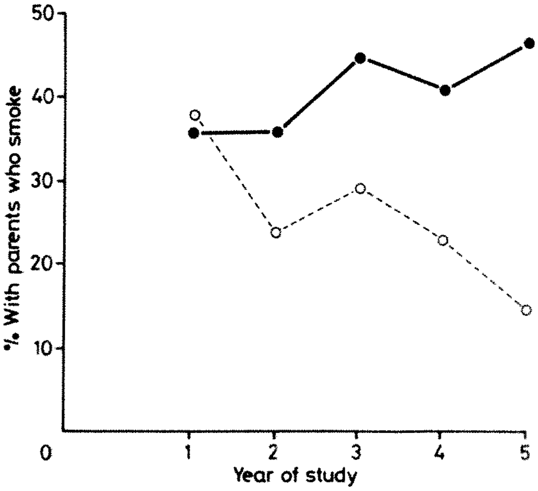

Fig. 6 *Parental smoking habits and wheezing in the atopic study population.* ●——●=*Atopic children with wheeze (n=22);* ○– – –○=*atopic children without wheeze (n=26).*

Table 3 *Virus isolations in 48 symptomatic children with atopy in first year of life*

Wheezy children			*Non-wheezy children*		
Isolates		*No*	*Isolates*		*No*
Rhinovirus	Type H	2	Rhinovirus	Type M	2
Para-influenza	3	3	Para-influenza	3	3
Influenza	A	1			
Respiratory syncytial virus		1	Respiratory syncytial virus		1

would develop allergic disease proved to be correct.[13] The predominant clinical problem was eczema, although most of the children were affected in the first two years only. Over 40% of the children had one or more positive results to a skin test, a prevalence in agreement with a previous report on similar children.[14] Most of the children with eczema were atopic, supporting an association between disease expression and the genetic predisposition to develop IgE antibody responses. The most commonly identified skin sensitivity in the first year was to egg protein. The skin reaction was often transient, disappearing in the second year at a time when the prevalence of eczema was also decreasing. These results suggest a role for food specific immune responses in the pathogenesis of infantile eczema, as has been suggested by others. Skin reactivity to inhalant allergens represented the predominant sensitivity in older children with eczema, although it developed later than that to foods. The role of inhalant allergens in the pathogenesis of eczema has received somewhat less attention. It has been shown that the raised IgE concentrations of children and adults with this disorder includes inhalant allergen specific IgE antibody.[15] The presence of this antibody is not explained by concomitant respiratory allergic disease. Furthermore, the application of such allergens to the skin has been shown to induce eczematous lesions in sensitive individuals.[16] Both ingested and inhaled allergens are probably of clinical importance in subjects with eczema, though their predominant effects may be at different stages of development.

In this study the children who wheezed on four or more occasions all showed evidence of atopy. The predominant sensitivity was to the major inhaled allergens. The results suggest that this preschool chest disorder is indistinguishable from asthma. Not all atopic children develop asthma, suggesting that atopy alone does not give rise to symptoms. Children who wheeze once only in the early months of life do not necessarily go on to show evidence of atopy, and their IgE concentrations are the same as those children who have no episodes of wheeze. Such episodes are usually associated with coryzal symptoms, suggesting that a single episode of wheeze can result directly from respiratory infection of this age.

As in our earlier report,[3] we were again unable to confirm the observation that children with atopic symptoms had a transient deficiency of IgA concentration at 3 months.[17] Differences in study design, clinical definitions, and duration of follow up may account for the conflicting results. We were unable to show that either month of birth or social class influenced the onset of asthma, but it would require much longer epidemiological studies[18 19] to detect this influence.

This study confirms other observations that respiratory viruses can be isolated from young children during episodes of wheeze.[20 21] The same viruses were isolated, however, from children with coryzal symptoms in both atopic and non-atopic children. These findings suggest that viral infection against an atopic background does not adequately explain all symptoms. No virus, or group of viruses, could be identified as more asthmagenic than others. Due to sampling difficulties in older children, this study was unable to confirm the role of viral infections in the development of recurrent wheezing.

It is known from epidemiological studies that exposure to cigarette smoke doubles the risk to the infant of an attack of pneumonia or bronchitis.[22] Our study suggests that this risk is not confined to infancy and parental smoking habits but may have an even stronger influence on the pathogenesis of wheezing in the 5 year old child. The mechanism of this effect is unclear. In adults smoking may result in an increase in bronchial hyperactivity,[23] this change being only weakly dependent on the atopic state of the patient. Immunological variables can be altered in smokers, including a rise in IgE concentrations. In this study the children of parents who smoked did not show raised IgE concentrations, perhaps suggesting a different mechanism. We have reported elsewhere that the immune response to house dust mite was increased in those children exposed to higher concentrations of its major allergen, antigen p1.[10] These differences include prevalence of skin test reactivity and radioallergosorbent test specific for *D pteronyssimus*. It has been shown previously that avoidance of house dust mite both in children and young adults can result in a reduction of bronchial hyperactivity.[24 25] It is quite clear that recurrent wheezing develops in these subjects who are genetically predisposed to develop an atopic state. It is possible that cofactors, or environmental influences, such as parental smoking, house dust mite antigen, and respiratory tract infections, either by a direct effect on airway reactivity or by altering the nature of the immune response to particular allergens, are required to allow disease expression. The possibility of a synergistic effect between these factors must also be borne in mind.

Breast feeding failed to show any protective effect against the development of allergic disease, including eczema. Whether breast feeding affords protection against atopic disease remains controversial.[3–6] Random controlled clinical trials have given conflicting results. As it is difficult to control how mothers feed their babies many studies have been of an observational design. Our study can be criticised on these grounds. Bias may have arisen if those infants most at risk opted into the breast feeding group. As the risk was equal among all babies this seems to be unlikely. Moreover, the number of breast fed babies in the trial was similar to local practice at the time. Observer bias was minimised by the clinician being unaware of the feeding history at the time of the clinical assessment. Our conclusions are similar to other recent reports.[7,8]

The finding that egg sensitivity, as shown by immediate skin test reactivity, can occur in wholly breast fed babies suggests that maternal diet may be of relevance. Food allergies in fully breast fed infants have been described.[26] It has been shown in experimental rats that repeated low dose exposure through breast milk increases the likelihood of developing an IgE antibody response to a food protein.[27] The increased incidence of skin tests positive to egg, in breast fed babies compared with bottle fed babies, during the past six months suggests that similar events may occur in man. While breast feeding should continue to be recommended by paediatricians as the best available feed for most babies, we do not believe that it can be promoted as a preventative measure in those infants at risk of developing allergic disease. Studies on the role of maternal exclusion dieting while breast feeding are indicated.

In conclusion, the development of asthma and eczema in susceptible children seems to be influenced by a wide variety of environmental factors. The issue of dietary exposure is as yet unresolved. Exposure to inhalant allergens such as the house dust mite can be reduced, although it is not clear what level of reduction is required to alter the natural history of the disease.[28] The simplest advice that we can give the parents of atopic children is to stop smoking in the child's presence.

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Prodromal features of asthma

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SUMMARY One hundred and thirty four ambulatory children with bronchial asthma were investigated in the Pediatric Pulmonary-Allergic Service. In 95 patients an interval characterised by prodromal respiratory symptoms (cough, rhinorrhoea, and wheezing), behavioural changes (irritability, apathy, anxiety, and sleep disorders), gastrointestinal symptoms (abdominal pain and anorexia), fever, itching, skin eruptions, and toothache preceded the onset of the attack of asthma. Each child had his own constant set of prodromal findings.

A significant age related increase in serum IgE concentrations was observed in these patients. No such relation was observed in children with an acute onset of attack of asthma without any preceding symptoms. We suggest that awareness of these prodromal symptoms may lead to an early introduction of treatment, thus avoiding or abbreviating some of the acute attacks of asthma.

The overt attack of asthma is often preceded by a variety of prodromal symptoms, some of which are not related to the respiratory system.[1-4] The aim of this study was to characterise these prodromal findings and thus enable an early introduction of treatment for asthma, an approach that may, in some patients, either avoid or abbreviate the attack of asthma.

Patients and methods

One hundred and thirty four patients (90 boys and 44 girls), presenting to the outpatient clinic of the Pediatric Pulmonary–Allergic Service at our centre, were studied. Mean (SD) age was 7·0 (1·8) years (range 1·5–14 years). Ninety three had seasonal and the remaining 41 perennial bronchial asthma. All the patients had bronchial asthma based on the criteria set by the American Thoracic Society.[5]

A standardised questionnaire that recorded the symptoms that preceded the attack of asthma was completed by the parents. The attack of asthma was defined as an acute onset of noisy breathing associated with wheezing, tachypnoea, and intercostal and/or suprasternal retractions. Symptoms preceding the attack of asthma, such as rhinorrhoea, cough, fever, skin eruption, irritability, apathy, anxiety, sleep disorders, loss of appetite, abdominal pain, itching, and toothache were recorded according to their chronological occurrence. Duration of asthma and total number of attacks and admissions to hospital during the last year were documented. The chronic or sporadic use of oral antihistamines, theophylline, steroids, or inhalation treatment with betasympathomimetics or sodium cromoglycate was recorded. To minimise errors due to the parents' memories, data recording was limited to the year preceding the first examination at our outpatient clinic.[3 6]

History of asthma, atopy, hay fever, or a specific allergic reaction to dust, pollen, or foods in either parents or siblings, or both, was considered positive only if diagnosed by a physician. Atopy was considered present if the patients had a personal and/or a family history of an atopic condition (eczema, hay fever, food allergy, or asthma) and a positive prick test to one or more of 10 common allergens. An asthma history severity score from 1 to 4 was computed for each child as described by Murray *et al.*[6]

Determination of serum IgE concentrations was performed during the symptom free intervals while children were on treatment with bronchodilator alone or without prophylactic treatment. Serum samples were stored at −20°C until analysed. IgE was assayed by a commercial solid phase radioimmunoassay (Prist, Pharmacia Ltd, Uppsala, Sweden).

Statistical analysis was performed by Student's *t* or Fisher's exact tests. Due to the considerable variation, IgE concentrations were transformed into logarithmic values and presented as geometric means. The Pearson coefficient was used to test the correlation between the log (IgE) and the age of the patients and p for the null hypothesis was obtained from statistical tables.[7]

Results

The study comprised 134 children attending the outpatient service. In 91% of the patients with seasonal asthma and 34% of the patients with perennial asthma the acute attacks occurred from March to June and from September to November. The duration of asthma ranged from one to seven years.

The patients were divided into two distinct groups according to the presence or absence of prodromal symptoms preceding the overt attack of asthma by hours or days. Group A comprised 95 (71%) patients who showed prodromal symptoms six hours or more before the attack of asthma. Group B comprised 39 (29%) patients with a rapid evolution of symptoms that led to the overt attack of asthma within six hours. No significant difference in any of the variables listed in Table 1 was observed between the two groups. In group A the mean (SD) number of prodromal symptoms per patient was 2·84 (0·86) and the mean (SD) interval between the occurrence of the initial prodromal symptom and the overt attack of asthma was 23·5 (11·1) hours. The patients were classified according to the occurrence of the initial prodromal symptoms in time ranges of six to 12, 12 to 24, 24 to 36, 36 to 48, and 48 to 60 hours before the onset of the overt attack of asthma. In computing time averages and standard deviations the mean of a range was taken to represent the time of occurrence of the individual prodromal initial symptom.

The type of the initial prodromal symptom and its time relation to the overt attack of asthma is recorded in Table 2. As shown the most common symptoms (62%) were related to the respiratory tract (rhinorrhoea and cough), which were followed in frequency (20%) by behavioural changes (irritability, apathy, anxiety, and sleep disorders). Fever, gastrointestinal symptoms (loss of appetite, and abdominal pain), itching sensations, skin eruptions, and toothache were fairly rare. In 92 (97%) of the patients the initial symptoms was followed by additional ones; they were polysymptomatic and usually more than one system was involved (Table 3). Any given child presented with a constant initial symptom and a characteristic set of additional prodromal findings. Not all the additional prodromal findings were present, however, during any given attack of asthma. Eighty two (86%) of the 95 patients in group A constantly showed the same prodromal features before each attack of asthma, while the other 13 (14%) showed a variable number of prodromal symptoms in each subsequent attack of asthma.

Table 1 *Comparison of individual characteristics in patients with (group A) or without (group B) prodromal symptoms before the attack of asthma*

	Group A (n=95)	*Group B (n=39)*
Sex (M:F)	66:29	24:15
Mean (SD) age (years)	6·7 (2·8)	7·7 (3·6)
No of patients with family history of allergy	56	24
Mean No of admissions per patient during the last year	0·55	0·56
Mean (SD) No of attacks of asthma per patient during the last year	6·8 (2·6)	7·3 (2·4)
Type of asthma:		
Seasonal	68	25
Perennial	27	14

Table 2 *Initial prodromal symptom and its time relation to the overt attack of asthma*

Symptom	*No of patients*	*Interval (hours) between initial symptom and onset of overt attack*	
		*Mean (SD)**	*Range*
Rhinorrhoea	39	26·76 (12·00)	6–60
Cough	23	20·73 (0·42)	6–48
Irritability	7	28·28 (4·53)	12–36
Apathy	7	28·28 (4·13)	12–36
Anxiety	3	30	24–36
Sleep disorders	2	18	12–24
Fever (above 38°C)	5	16·2 (4·0)	6–24
Abdominal pain	2	13·5 (6·4)	6–24
Loss of appetite	2	18	12–24
Itching	3	9	6–12
Skin eruption	1	9	6–12
Toothache	1	9	6–12

*The means and standard deviations were computed according to average representative values of the appropriate time ranges.

Sixty two patients whose initial prodromal symptoms were respiratory in nature—that is, rhinorrhoea or cough—had a mean (SD) age of 7·3 (2·8) years and a mean (SD) interval between the initial symptom and the overt attack of asthma of 24·5 (12·2) hours. The 33 patients in group A whose initial symptoms were not of a respiratory nature had a mean (SD) age of 5·2 (2·1) years and a mean (SD) interval between the initial symptom and the overt attack of asthma of 21·5 (8·5) hours. The prodromal symptoms were observed by the mother in 64 (67%) patients, by the father in 12 (13%), and by both parents in 19 (20%).

In 30 (77%) of the 39 patients in group B the initial symptom occurred half an hour to an hour

Table 3 *Relation of initial prodromal symptom to additional ones preceding the overt attack of asthma*

*Initial prodromal symptom**	*Additional prodromal symptoms*						
	Rhinorrhoea	*Cough*	*Behaviour changes*	*Fever*	*Gastro-intestinal symptoms*	*Skin eruptions*	*Toothache*
Rhinorrhoea (39)	—	39	10	5	3	2	1
Cough (23)	11	—	6	5	1	2	1
Behavioural changes (19)	5	19	—	1	5	2	0
Fever (5)	3	5	1	—	0	0	0
Gastrointestinal symptoms (4)	2	4	2	0	—	0	0
Skin eruption (4) and itching	1	4	1	0	0	—	0
Toothache (1)	1	1	0	0	0	0	0

Numbers in parentheses refer to the number of patients presenting with the particular set of symptoms.

before the attack of asthma without any premonitory warning. In the remaining nine (23%) respiratory symptoms, seen as rhinorrhoea, cough, and strong wheezing, occurred one to six hours before the overt attack of asthma. The history asthma severity score was 2·18 (0·85) for the patients in group A and 2·15 (0·90) for those in group B.

Serum samples for the determination of IgE concentrations were available in 82 patients (53 of the 95 patients in group A and 29 of the 39 patients in group B). Sex distribution, mean age, and type of asthma were similar in these patients compared with those who had no serum samples available for IgE determinations. The interpretation of serum IgE concentrations in the 82 patients with serum samples available was therefore considered to be representative of the whole study group. No significant difference in the serum log (IgE) values between patients with (2·56 (0·32)) or without prodromal symptoms (2·64 (0·34)) was observed.

A significant age related increase in log (IgE) values was observed in patients who had prodromal symptoms; no such relation was observed in the patients in group B (Figure). Prick tests were performed in 65 of 118 patients with personal and/or family atopic history. Fifty three of them showed positive reactions to one or more allergens. Of these, 39 belonged to group A and 14 to group B ($\chi^2=0{\cdot}135$, p=not significant).

Discussion

The presence of prodromal symptoms preceding the overt attack in some of the patients with asthma has been recognised previously but not studied carefully.[1-4] These symptoms may not be confined to the respiratory tract alone and may often involve other systems as well. In 95 of the 134 patients followed by us the attack of asthma was preceded by prodromal features that were usually constant for any given patient. The most commonly affected system in our study was the respiratory tract, followed by behavioural changes. Other symptoms such as fever, abdominal pain, or skin eruption were rare. Itching, a common symptom in other studies,[2 3] was observed in only three patients, though this was probably due to the younger age of our population. The mean (SD) interval between the occurrence of the initial prodromal symptom and the attack of asthma was 23·5 (11·1) hours for the 95 patients with prodromal symptoms. The interval for patients whose initial prodromal symptom was of a respiratory nature was not significantly longer than for those whose initial prodromal

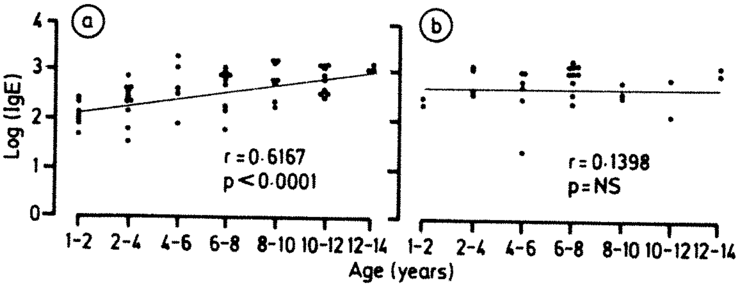

Figure *Individual serum IgE concentrations according to age in patients with (a) and without (b) prodromal symptoms.*

NS=Not significant.

symptom was not respiratory in nature ($p<0{\cdot}1$). Prodromal symptoms that were not of a respiratory nature were less common. They occurred in 33 (35%) patients as the initial symptom. The mean age in years of the patients with initial symptoms of a respiratory nature was significantly higher than that of the patients with initial symptoms of a non-respiratory nature ($p<0{\cdot}0005$). It is clear, therefore, that in younger patients the prodroma begins more often with initial symptoms that are non-respiratory in nature. A comparison of individual characteristics of patients with or without prodromal symptoms showed no significant difference in the type of asthma (seasonal or perennial), sex distribution, age, family history of allergy, or severity of asthma.

Weather changes and upper respiratory infection are associated with gradual onset of acute attacks of asthma.[1] Most of our patients with prodroma had their acute attack in changing weather periods. The rapid development of the acute attacks in the patients in group B may be due to specific, intermittent, but overwhelming allergic or irritant exposure.

As our study was a retrospective one some degree of mild bronchoconstriction, clinically unrecognisable by the parents, may have existed in some of our patients during their prodromal phase. Obviously, based on our questionnaire we cannot define the exact onset of the attack of asthma. As the vast majority of patients are treated at home, however, it seems, from a practical point of view, that parental recognition of these prodromal symptoms may lead to an early introduction of treatment, thus avoiding or abbreviating some of the attacks of asthma.

Serum IgE concentrations increased with age in patients with prodromal symptoms. In patients without any preceding symptom no such relation was observed. Whether this observation reflects a basic immunological difference that signifies a different development in the allergy pattern in the two groups of patients remains unclear.

It seems to us that the differentiation of the population with asthma into two groups according to the presence or absence of prodromal symptoms may lead to a different therapeutic approach. In children with an acute onset of asthma continuous prophylactic treatment may be indicated, whereas in children with preceding symptoms treatment may be introduced only at the onset of the initial prodromal findings.

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Influence of antacid and formulation on effectiveness of pancreatic enzyme supplementation in cystic fibrosis

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SUMMARY A series of treatment trials, involving food balances based on determination of fat coefficient absorption, nitrogen faecal loss, and daily faecal weight, was performed in 82 patients with cystic fibrosis.

Results showed that a conventional powdered pancreatic extract (Pancrex V) required a high dosage to achieve reasonable improvement in fat and nitrogen absorption (200 mg/kg body weight/day on average) and rarely restored digestion to normal. Bicarbonate (5·2 g/m^2 body surface/day) slightly enhanced the enzymatic activity of the powdered extract, this being more apparent in those with more severe steatorrhoea. There was no advantage in providing the extract in microgranules protected by cellulose acetatephthalate. A product based on fungal lipase and protease (Krebsilasi) proved to be ineffective in correcting fat and protein absorption. The two recent products prepared in pH sensitive microspheres (Pancrex V microspheres and Pancrease-Prolipase) had similar advantages in digestive activity. Compared with the traditional preparations, they offered a number of practical advantages, including a smaller number of capsules (particularly Pancrex V microspheres) and improved palatability.

Cystic fibrosis is by far the most common cause of pancreatic insufficiency in children.

The use of concentrated pancreatic extracts, obtained mainly from hog pancreas, has played a considerable part for many years in improving the nutritional state of fibrocystic patients.[1-5] But the limitations of conventional pancreatic extracts have become very apparent, especially in the management of steatorrhoea.[3-5] Inactivation by the peptic and acid secretion of the stomach plays a fundamental part in this. In the adult it has been shown that only 8% of lipolytic activity and 22% of proteolytic activity administered by mouth can be recovered from the loop of Treitz.[6] Digestion and absorption of lipids are then further impaired in this disease by deficient secretion of bicarbonate, preventing optimisation of intestinal pH for lipase activity and by deficient lipid micellation due to the reduced pool of bile acids, which are then reabsorbed poorly at the level of the ileum.[3 7]

Repeated attempts to overcome the gastric effects by formulating the extract in gastroresistant tablets or in granules coated with cellulose acetatephthalate have met with little success.

Few trials have been performed with enzymes of vegetable or bacterial origin, which would have the advantage of not being inactivated in an acid pH.[8 9] Lingual lipase, whose excellent activity in an acid medium is well known, has not yet been made available for therapeutic use.[10] Use of massive doses of extract has been the main means of overcoming gastric inactivation.[4] The combined administration of antacids (sodium bicarbonate, aluminium hydroxide, etc) or H_2 receptor antagonists, to reduce gastric acid secretion, has given conflicting results.[11-13]

A more favourable reception has recently been given to extracts made up in pH sensitive, gastroprotected, and enterosoluble microspheres. These microspheres are stable at pHs below 5·5 and hence the extract is not inactivated in the stomach, while the enzymatic activity is released in 15–30 minutes in an alkaline medium and hence is activated in the small intestine.[14] The small size of the microspheres (diameter less than 3 mm) also allows homogeneous distribution of the extract in the food. Several controlled clinical studies in patients with cystic fibrosis have shown the effectiveness of these extracts, even if the results are not in complete agreement. Some studies have shown that fat and protein absorption improves compared with conventional extract.[15-17] Others have produced results similar to those obtained with conventional extracts but with a definitely lower daily number of capsules and without the unpleasant taste of the powdered pancreatic extract, thus leading to better therapeutic compliance.[2 13 14 18]

Interpretation of these clinical trials is generally difficult because of the small number of patients studied, especially as it is a therapeutic field in which individual variability plays an important part in influencing the results. This study describes research into the possible beneficial effect of antacids, looks at any advantages of pancreatic extracts in pH sensitive microspheres, and compares the old and new extracts available on the market today, using a larger number of patients with cystic fibrosis.

Patients and methods

In all patients included in this study the diagnosis of cystic fibrosis was made on the basis of at least two sweat tests, using the Gibson and Cooke procedure.

In most of the patients a study was then made of pancreatic function by duodenal intubation, stimulation with a secretin-pancreozymin bolus (2 U/kg body weight), and determination of the enzyme and bicarbonate output for 30 minutes.[19] In addition, a food balance was carried out for three to four days, with determination of the coefficient of fat absorption (ACfat), faecal nitrogen loss, and daily faecal weight. The food balance during treatment with pancreatic extracts or antacids was made under hospital conditions: the start and end of each balance was marked by oral administration of carmine. During each balance a diet was given with strictly controlled fat content (from 2 to 4 g/kg/day according to age; average 3 g/kg/day), while the protein and carbohydrate content were balanced but uncontrolled. When pancreatic extracts were administered the number of capsules given each day was calculated and rounded individually around the chosen dosage, distributed over the four daily meals and divided during the meal into start, middle, and end. When two extracts were compared in the same subjects priority was randomly assigned.

The following variables were recorded for the faeces in each period: faecal fats by Van de Kamer's method, as modified by Jeejeebhoy for medium chain triglyceride fats,[20] with calculation of the coefficient of absorption, and daily faecal nitrogen determined on a Carlo Erba ANA automatic analyser.[21] The means of the results obtained for paired groups were compared by Student's *t* test.

Consent was obtained from the parents or patients, or both, after adequate explanation.

The declared characteristics and composition of the different pancreatic extracts used are set out in Table 1.

The gastroprotective coating of the two pH sensitive compounds is made from cellulose acetatephthalate, plasticised with diethylphthalate. Of the other excipients, which are the main constituents of microsphere cores, the composition was available

Table 1 *Declared characteristics and composition of the different pancreatic extracts used*

Pancreatic extract (Manufacturers)	*Form of preparation**	*Weight of contents of one capsule (mg)*	*Declared active substance*	*Declared content of FIP‡ units in one capsule*		
				Lipase	*Amylase*	*Protease*
Pancrex V powder (Samil-Pabyrn)	Powder (in capsules)	340	Pig pancreatin BP 340 mg	13000	10500	550
Pancrex V granular (Samil-Pabyrn)†	Gastroresistant microgranules (cellulose acetate-phthalate) in capsules	500	Pig pancreatin BP 420 mg	15000	13000	680
Pancrex V microsphere (Samil-Pabyrn)	Gastroresistant, enterosoluble, pH sensitive microspheres in capsules	500	Pig pancreatin BP 340 mg	13000	10500	550
Pancrease-Prolipase (Cilag)	Acid resistant, enterosoluble, pH sensitive microspheres (in capsules)	420	Pig pancrelipase	5000	2900	330
Krebsilasi (Irbi)	Separate tablets (in capsules)	500	Ox pancreatin and fungal enzymes	7500	9000	350

*All the enzymatic preparations are contained in hard gelatin capsules
†The granular preparation in the Italian market has different characteristics from a similar preparation in Britain.
‡FIP=Federation Internationale Pharmaceutique.

for the Pancrex V microspheres* only—namely, amidocarboxyethylate, polyvinyl pyrrolidone, saccharose, starch, talc, and E171.

The dosage of pancreatic extracts was standardised on the basis of our previous study,[4] in which a relation between dose and effect was found for Pancrex V powder: 200 mg/kg/day, corresponding to about 75 mg of extract per gram of fat administered, resulted in the most acceptable and reasonable dose. Adequate adjustments were made for the new preparations Pancrease-Prolipase and Pancrex V microspheres.

The overall study was made in successive stages as briefly described below.

Phase I: effect of sodium bicarbonate. The effect of sodium bicarbonate in combination with Pancrex V powder was tested in 40 patients with cystic fibrosis. Of these, 26 (mean (SD) age 5·09 (4·12) years) were treated with this conventional extract and then with the same extract plus sodium bicarbonate (5·2 g/m^2 body surface/day). The other 14 (mean (SD) age 5·56 (4·05) years) constituted the control group, in whom the only treatment, alternating with two basal balance phases, was sodium bicarbonate.

Phase II: comparison between conventional powdered pancreatic extracts and gastroresistant granules. Pancrex V powder and Pancrex V microgranules† were compared in six patients with cystic fibrosis (mean (SD) age 10·2 (5·3) years) according to the same dosage as in phase I.

Phase III: comparison between conventional powdered pancreatic extracts and extracts in pH sensitive, gastroprotected, and enterosoluble microspheres. Three comparative trials were made in succession (Table 2).

(A) Pancrex V powder versus a pH sensitive extract (Pancrease-Prolipase) in 11 patients with cystic fibrosis (mean (SD) age 9·5 (4·2) years) with the same quantity of extract by weight.

(B) Pancrex V powder versus a second pH sensitive extract (Pancrex V microspheres) in 10 patients with cystic fibrosis (mean (SD) age 8·3 (4·7) years). For Pancrex V microspheres it was decided to administer a dose that would provide lipase activity equal to that of the administration of Pancrease-Prolipase in the preceding group.

(C) The first (Pancrease-Prolipase) versus the second (Pancrex V microspheres) pH sensitive extract in 10 patients with cystic fibrosis (mean (SD) age 10·6 (6·1) years). The dosage used for Prolipase-Pancrease was 70–100 mg/g fat and for Pancrex V microspheres was a quantity by weight that would supply the same activity as the preceding extract (35–50 mg/g fat).

It should be pointed out that, in view of the presumed advantages of the pH sensitive compounds, the quantity of lipase activity administered with these corresponded to about a third of the lipase activity of Pancrex V powder.

For the preparations administered to infants unable to swallow capsules, the microspheres were mixed with grated apple, which has an acid pH: this procedure did not create any problems.

Phase IV: pancreatin with enzymes of fungal origin. The digestive effect of the product Krebsilasi (pancreatin with enzymes of fungal origin) was studied, with the criteria previously described, in five patients with cystic fibrosis (mean (SD) age 8·1 (1·8) years) in comparison with their baseline digestive situation. With regard to dosage, the mean (SD) quantity of capsules (12 (1·7) per day) administered each day was such as to supply a lipase activity roughly equal to that of the pH sensitive formulations (1496·4 (277·8) FIP (Federation Internationale Pharmaceutique) lipase units per gram of fats administered).

Results

Effect of bicarbonate. Figure 1 shows individual and

Table 2 *Treatment schedule with different pancreatic extracts in five groups of patients. Values are mean (SD) [range] except where stated*

Group	*No of patients*	*Baseline ACfat (%)*	*First pancreatic extract*	*Mean (SD) No of capsules/day*	*ACfat (%)*	*Faecal nitrogen (g/day)*	*Faecal weight (g/day)*	*Second pancreatic extract*	*Mean (SD) No of capsules/day*	*ACfat (%)*	*Faecal nitrogen (g/day)*	*Faecal weight (g/day)*
1	6	36·2 (16·6) [21·6–65·8]	Pancrex V powder	16·3 (3·3)	65·7 (16·8) [35·7–82·8]	2·73 (1·17) [1·41–4·74]	265 (159) [137–601]	Pancrex V microgranules	16·3 (3·3)	68·1 (22·1) [30·7–87·2]	2·23 (1·30) [1·21–5·09]	216 (131) [124–507]
2	11	41·1 (14·7) [19·0–73·0]	Pancrex V powder	16·3 (2·0)	70·7 (21·6) [22·3–93·7]	2·03 (1·14) [0·85–4·50]	207 (90) [79–442]	Pancrease-Prolipase	14·0 (1·7)	86·2 (13·5) [47·3–97·2]	1·40 (0·26) [1·10–2·09]	168 (37) [107–259]
3	10	48·8 (15·8) [25·0–65·6]	Pancrex V powder	16·8 (3·8)	78·2 (16·2) [52·1–96·7]	1·46 (0·37) [0·87–2·20]	137 (57) [77–228]	Pancrex V microspheres	7·0 (1·0)	83·9 (11·8) [55·2–96·0]	1·59 (0·44) [1·01–2·37]	177 (52) [115–292]
4	10	44·3 (18·9) [27·0–66·2]	Pancrease-Prolipase	14·6 (3·4)	87·3 (6·3) [73·3–93·9]	1·98 (0·98) [0·78–3·81]	181 (97) [72–420]	Pancrex V microspheres	6·6 (1·2)	86·5 (7·6) [66·9–95·4]	2·09 (1·46) [0·90–5·85]	162 (96) [73–384]

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*Pancrex V microspheres are not commercially available at the time of writing.

†Pancrex V microgranules in capsules are an experimental formulation not commercially available.

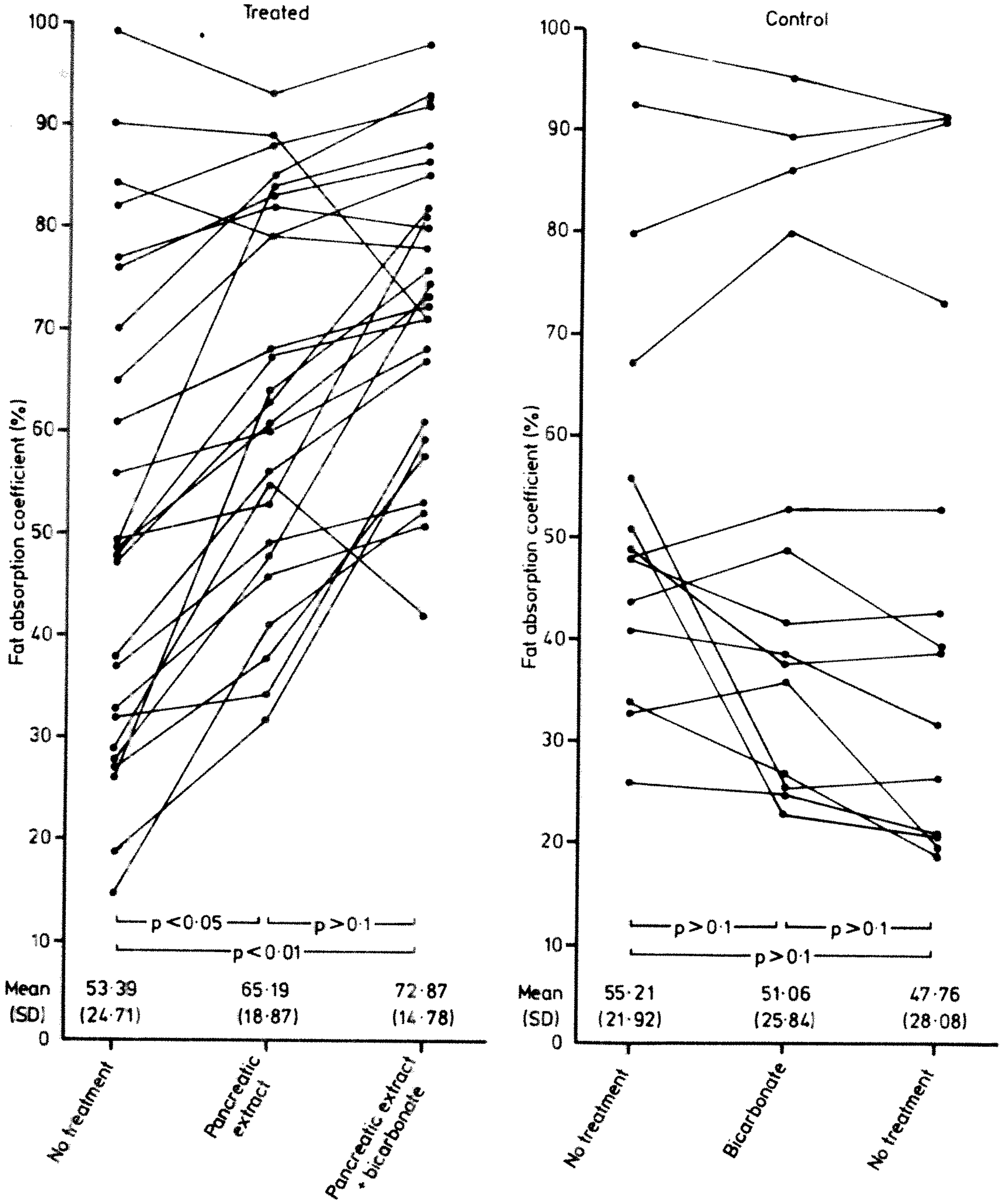

Fig. 1 *Fat absorption coefficient, obtained by three subsequent food balances in different treatment conditions in two groups of patients with cystic fibrosis. The 'treated' group received pancreatic extract (Pancrex V powder, about 200 mg/kg body weight/day) or pancreatic extract (Pancrex V, same dose) plus sodium bicarbonate (about 5·2 g/m^2 body surface/day); the 'control' group was treated with sodium bicarbonate alone (5·2 g/m^2 body surface/day).*

mean changes obtained in ACfat in patients with cystic fibrosis through the effect of pancreatic extract (Pancrex V powder) and through the effect of combining sodium bicarbonate with the extract, in comparison with a group of patients with cystic fibrosis treated with sodium bicarbonate alone. It is clear that by itself bicarbonate did not produce any effect, while its effect in combination with the extract was measurable but of little importance. There was a wide variation in response, presumably linked to the baseline absorption condition. Bicarbonate seemed in fact to have an enhancing effect on lipase activity, which was higher for patients with lower baseline ACfat; in patients with a baseline ACfat over 75% bicarbonate proved to be completely ineffective. Figure 2 shows individual and mean changes obtained for daily nitrogen loss in the same groups of subjects under the same treatment conditions. There was the usual wide variability of results, evident even in the control group.

Combining bicarbonate with the extract did not seem to affect the degree of azotorrhoea found with the extract alone. No change was observed in acid base equilibrium of the blood with the bicarbonate dosage used.

Comparison between two commercial forms of concentrated pancreatic extract (powder and micrograules). The results showed no differences between the mean values of ACfat, azotorrhoea, and daily faecal weight (Table 2). In view of these results, a fuller comparison was not made.

Evaluation of pancreatic extracts in gastroresistant and enterosoluble microspheres. (Fig. 3) The mean value of ACfat was about 86% with Pancrease-Prolipase compared with 71% with the conventional Pancrex V powder (p<0·05); there was no significant difference, on the other hand, as regards faecal nitrogen and daily faecal weight (Table 2). The ACfat obtained with Pancrex V microspheres was on average higher than that obtained with Pancrex V powder, even though the difference was not significant. There were no significant differences as regards azotorrhoea and daily faecal weight (Table 2).

In 10 patients the direct comparison between Pancrease-Prolipase and Pancrex V microspheres showed similar results for ACfat (average 87% and 86%, respectively), faecal nitrogen (mean 1·98 g/day and 2·09 g/day, respectively), and daily faecal weight (180 g/day and 160 g/day, respectively).

When the individual cases were examined the results were still similar.

Cumulative results. The overall data of the comparative clinical trials covered by the last two subheadings are summarised in Table 3, combining the cases from all treatment groups.

It can be seen that the pH sensitive formulations were more effective than the conventional ones as regards fat absorption, while there was no significant difference for loss of faecal nitrogen or daily faecal weight. Likewise, the comparison between the conventional powdered extract and its form in gastroprotected microspheres (Pancrex V), which showed no significant differences in the small trial, showed definite advantages for the microsphere form when all patients were considered together.

This effect was obtained with a lower activity of lipase per gram of fat and a decidedly smaller number of capsules each day. With the new gastroprotected and enterosoluble compounds mean ACfat values of about 85% were obtained: out of a total of 31 patients and a total number of 41 food balances, during which one or other of these extracts was administered, the improvement in digestion was excellent (ACfat over 90%) in 18, good (ACfat

Table 3 *Cumulative comparison between four types of pancreatic extract, with determination of fat absorption coefficient (ACfat), daily faecal nitrogen, and daily faecal weight (74 food balance tests in 37 patients with cystic fibrosis)*

Pancreatic extract	*No of food balance tests*	*Mean (SD) age (years)*	*Mean (SD) No of capsules/kg/day*	*Mean (SD) FIP lipase units per gram of fat administered*	*Mean (SD) FIP protease units per gram of fat administered*	*Mean (SD) [range] baseline ACfat (%)*	*On treatment (mean (SD) [range])*		
							ACfat (%)	*Faecal nitrogen (g/day)*	*Faecal weight (g/day)*
Pancrex V powder	27	9·2 (4·7)	0·74 (0·20)	3313·1 (506·9)	140·1 (21·4)	47·8 (16·5) [18·3–79·1]	72·3 (19·3) [22·3–97·1]	1·97 (1·05) [9·85–4·74]	194·1 (111·9) [77–601]
Pancrex V microgranules	6	10·2 (5·3)	0·70 (0·15)	3182·0 (477·8)	166·4 (24·9)	36·2 (16·6) [18·3–65·8]	68·1 (22·1) [30·7–94·4]	2·23 (1·30) [1·21–5·09]	216·4 (131·0) [124–507]
Pancrease-Prolipase	21	10·0 (5·2)	0·54 (0·18)	1034·8 (180·2)	68·2 (11·8)	42·8 (17·2) [4·0–73·0]	86·7 (10·7) [47·3–97·2]	1·68 (0·76) [0·78–3·81]	174·1 (72·4) [72–420]
Pancrex V microspheres	20	9·4 (5·5)	0·25 (0·14)	1327·7 (457·6)	56·1 (19·3)	46·4 (17·7) [4·0–79·1]	85·2 (10·0) [55·2–96·0]	1·84 (1·10) [0·90–5·85]	169·5 (77·7) [73–384]

Comparison of means between treatments (S=significant (p<0·05); SS=highly significant (p<0·01); NS=not significant (p>0·05)):

	ACfat:	Faecal nitrogen:	Faecal weight:		ACfat:	Faecal nitrogen:	Faecal weight:
1 *v* 2	p>0·6 (NS)	p>0·6 (NS)	p>0·8 (NS)	2 *v* 3	p<0·05 (S)	p>0·3 (NS)	p>0·4 (NS)
1 *v* 3	p<0·01 (SS)	p>0·2 (NS)	p>0·4 (NS)	2 *v* 4	p<0·05 (S)	p>0·5 (NS)	p>0·4 (NS)
1 *v* 4	p<0·01 (SS)	p>0·6 (NS)	p>0·3 (NS)	3 *v* 4	p>0·6 (NS)	p>0·5 (NS)	p>0·8 (NS)

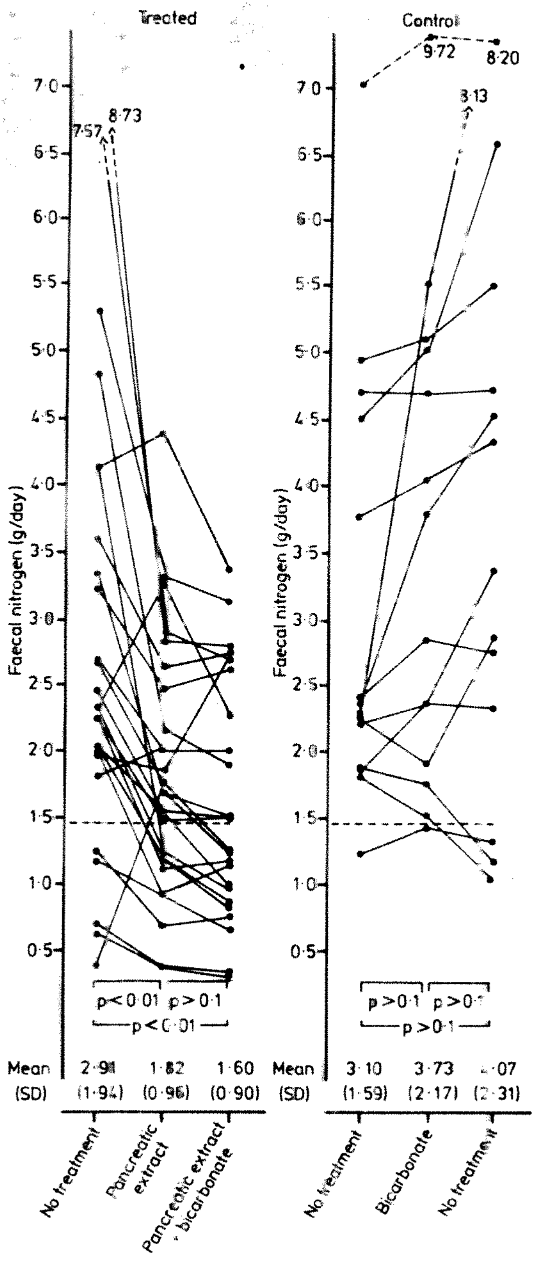

Fig. 2 *Daily faecal nitrogen determined by three subsequent food balances in different treament conditions in two groups of patients with cystic fibrosis. The 'treated' group received pancreatic extract (Pancrex V powder, about 200 mg/kg body weight/day) or pancreatic extract (Pancrex V, same dose) plus sodium bicarbonate (5·2 g/m² body surface/day); the 'control' group was treated with sodium bicarbonate alone (5·2 g/m² body surface/day).*

75–90%) in 18, and insufficient (ACfat lower than 75%) in only five.

With the conventional extract, out of a total of 27 treated patients and a total number of 27 food balances, there were only six in whom the ACfat was over 90%, while in seven it was between 75 and 90%, and in 14 it was well below 75%.

Evaluation of a product containing fungal lipase and protease (Krebsilasi). Baseline ACfat was not modified at all by this product (from a mean (SD) of 47 (15·5) % to 49·5 (13·6) %); faecal nitrogen improved to a very limited extent (from a mean (SD) of 4·82 (1·5) g/day to 3·82 (2·2) g/day) compared with the results obtained from the other products. A similar trend was observed for daily faecal weight (from 357·7 (102·8) g/day to 246·4 (55·4) g/day). There was no significant difference in the variables measured between the baseline situation and after treatment.

Discussion

By using bicarbonate with a conventional extract it is possible to obtain an improvement in the digestive effect of the extract on fats, though this is limited. The effect is greater when the baseline steatorrhoea is more severe, and it is quantitatively comparable with that obtainable with cimetidine.[11-13] No improvement in azotorrhoea can be obtained with bicarbonate. On the other hand, the overall faecal loss of nitrogen with the conventional extracts at high doses approaches closely to normal loss.

The preparations formulated to protect the extract against gastric inactivation were therefore considered with interest. Simple protection with cellulose acetatephthalate, as in the Pancrex V microgranules preparation, did not show any advantage. On the other hand, the preparations in pH sensitive gastroresistant and enterosoluble microspheres manufactured using more up to date methods were shown in our work to offer advantages. This conclusion was based on a larger set of cases than has generally been reported previously.[2 13 14 16-18] Such preparations were undoubtedly more active in promoting fat absorption than the unprotected extracts. No improvement was evident, however, in loss of faecal nitrogen or daily faecal weight.

These results should be compared with those obtained by other workers, who have not always shown greater efficacy of the new types of formulation but only shown greater practicability.[2 13 18] In other words, they have usually stated that the same effect can be obtained with a smaller dose of pH sensitive extract compared with the conventional extracts.

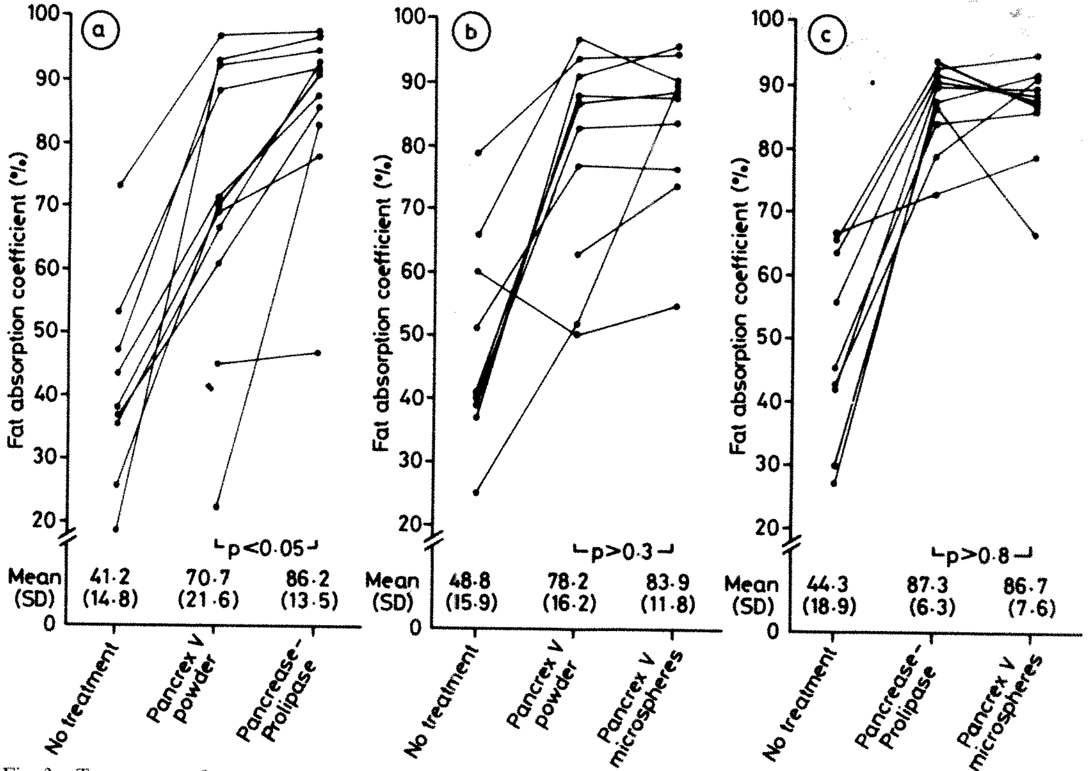

Fig. 3 *Two groups of patients with cystic fibrosis were treated alternatively with a conventional pancreatic extract and new pH sensitive formulations ((a) and (b), respectively)); a third group was treated with two different new formulations (c). Fat absorption coefficients on different treatments are compared with the baseline ones.*

Much of the reported work on pancreatic extracts has been based on excessively small samples.[2,13-18] In none of the experiments was the dosage related to the quantity of fats introduced, while evaluation of the results was often performed using ill defined variables.[17] It is acknowledged that this type of trial is somewhat difficult from the methodological standpoint. There is in fact great variability of results from case to case, and it is difficult to obtain well matched groups of patients. It is enough to observe that in our experiments three groups of subjects (numbering six, 11, and 10, respectively), treated with the same dosage of Pancrex V powder, gave three widely differing mean values for ACfat—namely, 65, 70, and 78%, respectively. Only comparing patients in large groups, as was made possible by the complex design of this experiment, allowed a reliable and statistically valid comparison to be made between the different pancreatic extracts.

We are unable to say whether the results obtained with recent extracts can be produced with even lower dosages than those used, but it must be reiterated that they were obtained with an intake of enzymatic activity of about a third of that which had given the best but not optimal activity with the powdered pancreatic extracts, on the basis of a progressive dosage test.[4]

The product based mainly on acid stable enzymes of fungal origin proved to be ineffective in correcting steatorrhoea and azotorrhoea in patients with cystic fibrosis.

Lastly, it should be pointed out that there are resistant cases (perhaps 10%) in whom no type of pancreatic extract nor any dietary addition can bring the digestion to acceptable equilibrium. These are the cases with either extensive ileal resection for meconium ileus or possible severe deficiency of resorption of bile acids.[7,13] In these cases we have found that inhibition of gastric acid secretion by means of H_2 antagonists has occasionally been successful, while there is the possibility of gaining some advantage by the use of bile salts to improve micellar concentration.

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Serum IgG antibodies in patients with cystic fibrosis with early *Pseudomonas aeruginosa* infection

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SUMMARY Serum IgG antibodies to *Pseudomonas aeruginosa* surface antigens were measured by enzyme linked immunosorbent assay in all patients with cystic fibrosis from whom *P. aeruginosa* was isolated for the first time during a study period of 18 months. In 15 patients the titre of serum IgG antibodies was greater than control values before or at the time of the first bacteriological isolation of *P. aeruginosa*. The presence of serum antibodies specific to *P. aeruginosa* suggests exposure to infection by that organism for some months before its isolation in significant numbers from the respiratory tract. In the other two patients serum titres were within the control range before isolation of *P. aeruginosa* but had increased to above the control range within the next month. Longitudinal studies on the entire group of patients showed further increases in titre concurrently with further isolations of *P. aeruginosa*. These results suggest that this assay may be an indicator of the beginning of pulmonary infection by *P. aeruginosa* and may prove to be a sensitive monitor of the progress of infection, and response to treatment, during the first months of infection by that organism.

Pulmonary infection by *Pseudomonas aeruginosa* remains a major cause of morbidity and mortality in patients with cystic fibrosis. Indeed, once *P. aeruginosa* is well established in the lungs it is rarely, if ever, completely eradicated, despite aggressive antipseudomonal chemotherapy.[1 2] In the early stages of pulmonary infection patients produce little or no sputum and bacteriological examination of the respiratory tract is commonly based on throat swabs. Even if sputum is produced, organisms that are present in low numbers are difficult to evaluate by available bacteriological techniques, and their significance may be in doubt. There is a need for a test to detect the presence of *P. aeruginosa* and to monitor the progress of the early stages of infection by that organism.

We have previously described an enzyme linked immunosorbent assay (ELISA) that measured free serum IgG antibodies against *P. aeruginosa* cell surface antigens. This was shown to be a specific and sensitive monitor of the progress of infection in patients with cystic fibrosis from whom *P. aeruginosa* had been isolated intermittently or continuously for at least six months.[3 4] In that study we found that most patients with cystic fibrosis (37 of 52) from whom *P. aeruginosa* had not been isolated had antibody titres within the range of control titres. We found a group of patients with cystic fibrosis, however, with antibody titres greater than control values but from whom *P. aeruginosa* had not yet been isolated. These patients were suspected of having early *P. aeruginosa* infection. In this paper we present data on serum anti-pseudomonal IgG titres in a prospective study on all patients from whom *P. aeruginosa* was isolated for the first time during a study period of 18 months.

Patients and methods

Patients. The patients attended the paediatric and adult cystic fibrosis clinics at our hospital. Their age range was 3–27 years (mean (SE) 11·8 (6·7) years). There were 14 girls and three boys. All had characteristic clinical features of the disease and had had at least one positive sweat test.[5] Analysis of previous results of bacteriological tests on these patients showed that *P. aeruginosa* had never been isolated from the respiratory tract, but the organism was isolated for the first time during the study.

Overall clinical state was assessed by the Shwachman score.[6] A maximum of 25 points was awarded for each of the following: chest *x* ray film, nutrition, general activity, and physical examination. Declining scores indicated a worsening condition. Chest *x* ray films were assessed by the Chrispin-Norman *x* ray score.[7] The possible scores were 0–38, an increasing score indicating an increasing abnormality.

Methods

Serum

At least two samples were available from 16 of the patients, the other patient having one sample available. Control serum samples were collected from 17 patients who attended the paediatric clinic and from whom blood specimens were taken surplus to requirements. The mean (SD) age for the control group was 9·54 (1·42) years. None had any evidence of infection caused by *P. aeruginosa*. All samples were stored at −20°C until immediately before use.

Enzyme linked immunosorbent assay (ELISA)

IgG antibodies to *P. aeruginosa* cell surface antigens were measured by ELISA as previously described.[3 4] Seven strains of *P. aeruginosa* with serotypes 1, 3, 6, 9, 10, and 11 and a strain that could not be typed were used.[8] These serotypes comprise most isolates (86%) from all our patients with cystic fibrosis and the serotypes of all isolates obtained from patients included in this study.

Results

During a study period of 18 months *P. aeruginosa* was isolated for the first time from 17 patients with cystic fibrosis. The serum IgG titres against *P. aeruginosa* were measured in these patients (Tables 1 and 2). The IgG titres were between 320 and 804 in 11 of the patients before the first isolation of *P. aeruginosa* from the respiratory tract and between 440 and 660 in four at the time of the initial isolation of that organism. Previous work in our laboratory has established that titres in paediatric patients without cystic fibrosis with no known *P. aeruginosa* infection were between 140 and 250, with an upper limit (99·9% confidence limits) of 270.[3 4] In these 15 patients with cystic fibrosis, therefore, the titres were greater than the normal range of control values before or at the time of the first isolation of *P. aeruginosa* from the respiratory tract. The earliest increase in titre was 18 months before the first isolation of that organism in one patient, but in most patients the interval was between one and 10 months. There was no correlation between titre and duration before isolation of *P. aeruginosa*.

The serum IgG titres were within the normal range during the months preceding the first isolation of *P. aeruginosa* in two of the patients (Table 2). Within one month of the first isolation, however, the titre had increased to greater than control values in both patients.

Further, intermittent, isolations of *P. aeruginosa* were obtained from all 17 patients. Ten (cases 1–10) received one or two courses of intravenous antipseudomonal treatment within six months of the first isolation of *P. aeruginosa* (Table 1). Intravenous treatment was followed by a partial decline in titre in five patients (cases 1–5), but *P. aeruginosa* was not eradicated from their sputum. In

Table 1 *Serum IgG titre to* Pseudomonas aeruginosa *in patients with cystic fibrosis before and after the first isolation from the respiratory tract. Figures in parentheses are time in months after isolation or treatment, as applicable*

Case No	*Age (years)*	*Sex*	*Before* P. aeruginosa *isolation*		*At first* P. aeragnosa *isolation*		*After* P. aeruginosa *isolation*		P. aeruginosa *isolation after treatment*	*Treatment*
			Months before first isolation	*Serum IgG titre*	*Shwachman score*	*FEV$_1$*	*Serum IgG titre*	*Serum IgG titre after treatment*		
1	14	F	11	317	90	98	713 (0·5)	420 (5)	Intermittent	C, F
			1	527						
2	12	F	5	390	90	94	1074 (1)	420 (7)	Intermittent	C, P, T, F
3	22	F	18·5	300	70		4780 (5·5)	3140 (2.5)	Continuous	T, A, F
			0	540						
4	22	F	1	324	60	74		274 (3·5)	Intermittent	T, A, F
5	11	F	0	590	75	33		512 (0·5)	Intermittent	T, A, F
6	3	F	2	490	80	145*		<140 (10)	None (8)	T, P
7	27	F	2	580	70	50		<210 (5·5)	None (3)	T, A
8	9	F	18	450	90	74		170 (1)	None (3)	T, P, F
9	15	M	16	320	85	76	340 (1)	190 (0)	None (1)	T, A, C
								140 (12)		
10	3	F	9	470	80	115		190 (5)	None (18)	T, P
								140 (8)		

Serum IgG titre refers to the sum titre to seven strains, with serotype 1, 3, 6, 9, 10, and 11 and a strain that could not be typed. C=Ceftazidime; P=pipercillin; T=tobramycin; A=azlocillin; F=flucloxacillin.

FEV$_1$=Forced expiratory volume in one second as % of value predicted for height.

*Peak expiratory flow rate as % predicted for height as patient too young for measurement of FEV$_1$.

Table 2 *Serum IgG titre to* P. aeruginosa *in patients with cystic fibrosis before and after the first isolation from the respiratory tract*

Case No	*Age (years)*	*Sex*	*Before* P. aeruginosa *isolation*		*At first* P. aeruginosa *isolation*		*After first* P. aeruginosa *isolation*	
			Months before isolation	*Serum IgG titre*	*Shwachman score*	*FEV$_1$*	*Months after first isolation*	*Serum IgG titre*
11	14	M	0	450	75	59	1	1020
12	10	F	0	410	80	75	17·5	700
13	13	F	0	660	70	76	No sample	
14	5	M	10	804	90	60	1	150†
15	4	M	6	336	90	100*	2	160†
			3	385			7	≤140
16	9	F	15	≤140	80	118	1	410
			7	≤140				
			0·5	≤140				
17	7	F	11	160	90	70	8	300
							17	720

Serum IgG titre refers to the sum titre to seven strains, with serotypes 1, 3, 6, 9, 10, and 11 and a strain that could not be typed.
FEV$_1$=Forced expiratory volume in one second as % of value predicted for height.
*Peak expiratory flow rate as % predicted for height as patient too young for measurement of FEV$_1$.
†Patients treated with continuous hydrocortisone.

the other five patients (cases 6–10) the titre decreased to within the control range in the months after intravenous treatment, and no further isolations of *P. aeruginosa* were obtained from their respiratory tract.

Four patients (cases 11, 12, 16, and 17) were not given intravenous treatment. *P. aeruginosa* was isolated intermittently from their sputum, and subsequent serum samples from all four patients showed an increase in IgG titre.

During the study, two patients (cases 14 and 15) began continuous treatment with corticosteroids. The IgG titre, which had been greater than normal, decreased to the lower level of detection within two months of beginning treatment with steroids. It remained at this low value for the next eight to 15 months, despite occasional isolations of *P. aeruginosa* from their sputum.

No further serum sample was available from one patient (case 13), although *P. aeruginosa* was isolated intermittently from sputum samples.

There was no significant correlation between the IgG titre of the entire group of patients described in this study with either the Shwachman score or the Chrispin-Norman *x* ray score, with the notable exception of case 3, in whom a severe infection was rapidly established.

Discussion

The results presented in this paper show that every patient with cystic fibrosis from whom *P. aeruginosa* had never been isolated but who had a serum IgG titre against *P. aeruginosa* greater than the control range subsequently had that organism isolated intermittently from the respiratory tract. In 11 of the 17 patients the serum IgG titre was greater than control values one to 18 months before the first isolation of that organism. A further four patients had significantly raised IgG titres at the time of the first isolation of *P. aeruginosa*. The presence of serum antibodies specific for *P. aeruginosa* in these patients suggests infection by that organism for some months before its isolation in significant numbers from the respiratory tract. Bacteriological examination of these patients often had to be based on throat swabs; but even if sputum is produced, organisms present in numbers less than 10^7 per litre are unlikely to be detected or considered significant by the semi-quantitative methods used in our laboratory. In addition, treatment with nebulised antibiotics may eliminate organisms from sputum samples but not necessarily all those present in the lungs.

The contribution of cross reacting antibodies to other Gram negative bacteria to this assay has been shown to be negligible.[3] This finding is in agreement with that of Kohler *et al*: in a radioimmunoassay using rabbit anti-pseudomonal serum to detect pseudomonal cells in urine, cross reaction with other Gram negative bacteria was also shown to be low.[9] We have previously shown that antibodies reacting with *P. aeruginosa* were present in very low numbers in patients without cystic fibrosis with no *P. aeruginosa* infection (between 140 and 250, with an upper limit (99·9% confidence limits) of 270).[3 4] This is also in agreement with the findings of other workers. Hoiby, using counterimmunoelectrophoresis and a sonicated antigen, showed that the prevalence of precipitating antibodies against *P. aeruginosa* increased gradually with age in a normal population.[10–12] The antibodies were present, only at low titres, however, in the normal population and were directed against two antigens that cross reacted with antigens from other bacterial species.[10–12] Cost *et al*, in a survey of 100 adults of unspecified age with no known *P. aeruginosa* infection, using ELISA, showed that serum antibodies against *P. aeruginosa* surface antigens were also present at low titres.[13]

Two of the patients in this study had titres within the control range before the first isolation of *P. aeruginosa*. Within about four weeks, however, the titre of both patients had increased to above control values. Given the delay in response by the humoral immune system, it would seem that *P. aeruginosa* was first isolated at an early stage of pseudomonal infection in these two patients.

Subsequent serum samples, available from seven patients, after the beginning of intermittent *P. aeruginosa* isolation but before intravenous antipseudomonal treatment, all showed further increases in titre. This increase suggests a continued antigen presence and further antigenic stimulus.

Ten of these 17 patients received intravenous antipseudomonal treatment. *P. aeruginosa* was not eradicated from the sputum of five patients, and although their IgG titres decreased, they were still greater than control values. In the other five patients intravenous treatment was followed by a decline in titres to within the control range, accompanied by no further isolations of *P. aeruginosa* from the respiratory tract, for between three and 18 months to date. This is in contrast with the effect of treatment on chronic *P. aeruginosa* infection, when long term eradication of the organism after treatment is an extremely rare occurrence.[1 2]

The lack of correlation between the IgG titre of the entire group of patients described in this study with either the Shwachman score or the Chrispin-Norman x ray score is perhaps not surprising for several reasons. Both scores are fairly crude measures of clinical state: the infection by *P. aeruginosa* in these patients was in the very earliest stages and so was unlikely to affect either of these scores. Furthermore, some of these patients had a well established *Staphylococcus aureus* or other bacterial infection, which will mask the small effects of the beginning of an infection by *P. aeruginosa*.

The antigen used in this assay was washed, intact cells being treated with glutaraldehyde. Antigens accessible for antibody binding are, therefore, lipopolysaccharides and those cell membrane proteins that are exposed to the surface, with glutaraldehyde forming crosslinks between amino groups.[17 18] The strain that could not be typed used in this assay often produced a significant titre, which may be due to antibodies directed against the core region of lipopolysaccharide, the cell membrane proteins, or other cell surface antigens. Although the cell membrane proteins are well conserved, they are present in different amounts in different strains.[19 20] A number of workers have reported serum antibodies to surface components other than the lipopolysaccharide side chain: antibodies specific to the core region of lipopolysaccharide were detected in the serum of 74% of patients with cystic fibrosis chronically infected with *P. aeruginosa*[21] and in rabbit immune serum.[22] Serum antibodies to outer membrane proteins have been shown in experimentally infected mice[23 24] and patients with cystic fibrosis chronically infected with *P. aeruginosa*.[21 25]

We have previously reported that this assay was a sensitive and specific measure of pulmonary infection by *P. aeruginosa* in patients with cystic fibrosis intermittently or chronically infected for at least six months. The immunological changes correlated with both the severity of infection and the clinical state of the patient.[3 4] Hoiby *et al*, using crossed immunoelectrophoresis and a sonicated preparation of *P. aeruginosa*, showed an increased number of serum precipitins against *P. aeruginosa* in patients infected for at least six months, and increased numbers of precipitins correlated with a worsening clinical state.[14–16] No such increase was detectable in patients infected for less than six months.[14–16] The results presented here show that the humoral response to pseudomonal infection can now be monitored during the first months of pseudomonal infection, as well as in the later stages, by ELISA.

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Nineteen hundred years ago

"We trained hard—but it seemed that every time we were beginning to form up into teams, we would be re-organised. I was to learn later in life that we tend to meet any new situation by re-organising, and a wonderful method it can be for creating the illusion of progress while producing confusion, inefficiency and demoralisation."

GAIUS PETRONIUS—AD 70.

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Plasma α fetoprotein reference ranges in infancy: effect of prematurity

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SUMMARY The dearth of plasma α fetoprotein reference ranges for preterm infants often impairs the clinical interpretation of plasma α fetoprotein data collected from ill babies. This study tested our hypothesis that meaningful plasma reference ranges could be established for preterm infants by a simple correction of patient age at sampling date for gestational age deficit at birth. Using a modified radioimmunoassay kit method, determinations of α fetoprotein were performed on capillary and venous blood samples collected from 56 babies aged from birth to 5 months with gestational ages ranging from 26 weeks to 43 weeks. Unmodified plasma α fetoprotein values were grouped according to patient age and examined statistically using established normal theory methods, but these yielded excessively wide reference intervals and non-Gaussian distribution parameters. Acceptable reference ranges were derived using logarithmic transformation of plasma α fetoprotein values and rearrangement against patient age corrected for gestational age deficit. These provisional reference ranges for plasma α fetoprotein in preterm (and term) infants are applied to groups of previously meaningless α fetoprotein results and used to test the potential usefulness of plasma α fetoprotein determination as a diagnostic marker in biliary atresia, hepatitis, and yolk sac derived tumours.

Alpha fetoprotein is a single chain α globulin, of molecular weight 68 000, normally unique to the fetus but often found in increased concentrations in plasma of children and non-pregnant adults with liver disease and some forms of malignant tumours. Alpha fetoprotein is produced in the developing fetus in equal amounts by the yolk sac and the fetal liver, but at about 12 weeks after conception the yolk sac degenerates and the fetal liver becomes the main site of synthesis. Fetal plasma α fetoprotein concentration reaches a peak value of 3 000 000 U/ml at a gestation of about 14 weeks.[1] Alpha fetoprotein synthesis almost ceases at parturition and the infant plasma concentration falls exponentially from a mean of 50 000 U/ml to a typical adult concentration of less than 10 U/ml at 6 to 8 months of age.[2]

The observation that α fetoprotein synthesis does not cease entirely at term[3-5] may be explained by the presence of fetal hepatocytes, which, though decreasing in number, sustain transient production of α fetoprotein during the early postnatal period. Any clinical condition that interferes with this physiological decline in fetal protein biosynthesis will disturb the usual fall in plasma α fetoprotein concentration. Such a mechanism has been postulated in neonatal viral hepatitis,[6] where compensatory proliferation of hepatocytes produces rapid regeneration of liver tissue and restoration of hepatic α fetoprotein synthesis.

Since the onco-fetoprotein α fetoprotein was first identified electrophoretically in the cord blood of human infants,[7] its merit as a general marker of perinatal disease has been studied intensively. The demonstration that this alpha migrating serum protein (otherwise detected in serum only during pregnancy) was identical in structure to a protein found in mice bearing transplanted hepatocellular carcinoma[8] was a major stimulus to interest in blood α fetoprotein as a potential tumour marker. This association was confirmed when patients with liver tumours, in particular hepatocellular carcinoma and hepatoblastoma, were shown to have increased serum α fetoprotein concentrations.[9]

Plasma α fetoprotein is now universally established as a reliable biochemical marker of malignancy not only for hepatic tumours but also for yolk sac derived tumours, some tumours of the gastrointestinal tract, and rarer teratocarcinomas with yolk sac elements, such as malignant sacrococcygeal teratoma.[10–13] A valuable feature of plasma α fetoprotein monitoring is its reported specificity[13] in detecting a small malignant yolk sac focus located in the midst of a 'benign teratoma'.

Clinical interpretation of plasma α fetoprotein concentrations in our term and preterm infants has been based predominantly on the graph of reference ranges published by Tsuchida *et al*, which takes no account of gestational age.[14] We have suspected for some time, however, that correction for gestational age deficit at birth would greatly enhance the clinical value of many plasma α fetoprotein results obtained in early infancy.

Patients and methods

Fifty six babies admitted to the neonatal surgical unit, Royal Hospital for Sick Children, and the paediatric department, Queen Mother's Hospital, from October 1984 to January 1985 were included in this study. At the time of sampling the infants were aged from birth to 5 months, with estimated gestational age at birth ranging from 26 to 43 weeks. Thirty seven preterm infants were studied. Fifty babies were singletons, four others comprised two sets of twins, and the remaining two were from two further twin pregnancies. A detailed list of the range of clinical conditions with disease incidences is available on request from the authors. Babies with conditions associated previously with abnormal plasma α fetoprotein concentrations—for example, six infants with sacrococcygeal teratoma—were excluded. In the case of two infants with gastrointestinal disorders and increasing serial plasma α fetoprotein concentrations only the initial α fetoprotein value was included for statistical analysis.

Residual plasma (typically 50–100 μl) from capillary and venous blood samples collected for routine biochemical analyses essential to patient care was used for estimation of α fetoprotein. These residual samples provided a single plasma α fetoprotein result for 34 patients; plasma was obtained twice from further blood samples in 13 others, and three to six serial (weekly intervals) α fetoprotein plasma samples were obtained for the remaining nine babies. Heparinised blood was spun, separated, and stored at 4°C until the primary analyses were completed and the plasma stored at −20°C, pending α fetoprotein analysis.[15] Study samples were included with batches of routine α fetoprotein determinations and handled in exactly the same manner as α fetoprotein requests for general diagnosis.

Assay method. Plasma α fetoprotein was measured using a routine 'tumour marker' assay based on the Amersham International AFP kit IM.984,[16] with the following modifications:

(1) Preparation of six additional standards by dilution of kit standards with the 'zero' standard to give 10 standards in the range 0–110 U/ml.
(2) Preincubation of standards and patient samples with anti-AFP serum for three hours at room temperature before addition of tracer.
(3) Aspiration of supernatants under mild vacuum (Venturi pump).
(4) All results with an α fetoprotein concentration of 3·4 U/ml or less reported as less than 4 U/ml.
(5) Appropriate dilution with the 'zero' standard and re-analysis of all specimens with α fetoprotein values greater than 100 U/ml.

Alpha fetoprotein results were reported in U/ml based on the International Agency for Research on Cancer Standard 72/225 (1 ng α fetoprotein=1·09 International Units).

Interassay imprecision expressed as percentage coefficient of variation was 3·9% at a mean α fetoprotein concentration of 50 U/ml and 3·5% at a mean concentration of 25 U/ml.

Statistical methods. Data reduction was achieved with the aid of a desk top minicomputer, using established normal theory methods on age grouped α fetoprotein results, which yielded the following statistics together with their standard errors and 95% confidence limits[17]: mean, median, standard deviation, and percentage coefficient of variation.

Previous studies on paediatric and adult α fetoprotein reference ranges prompted a simple logarithmic transformation of uncorrected α fetoprotein results and α fetoprotein results corrected for gestational age with re-application of the data reduction procedure. Linear ($Y=mX+c$) and exponential ($\ln(Y)=mX+\ln(c)$) least squares regression analyses were performed on ungrouped α fetoprotein data paired with both uncorrected and corrected patient ages.

Results

An essential prerequisite to the lengthy derivation of age related plasma α fetoprotein reference ranges was the verification of underlying relations between plasma α fetoprotein concentration and patient age. Linear and exponential least squares regression analyses were performed on the entire set of 97 plasma α fetoprotein values matched in the first instance with patient age at sampling and then with patient age corrected for gestational age deficit at birth (Table 1).

Results of linear regression analysis quickly confirmed earlier assumptions of a significant negative correlation (r=−0·42, n=97, p<0·01) between plasma α fetoprotein concentrations and uncorrected age. As expected the introduction of correction for gestational age produced a beneficial effect on the degree of correlation (r=−0·58, n=94, p<0·01) measured by linear regression. A remarkable doubling of the correlation coefficient, yielding an identical r value of −0·85 for both uncorrected data and data corrected for gestational age deficit, followed the application of exponential least squares regression. The latter findings were not attributable entirely to chance but could reasonably have been deduced from previous observations of the exponential fall in plasma α fetoprotein concentration with increasing age in term[2 14 18] and preterm[19] infants.

Although shortage of α fetoprotein data precluded the subsequent derivation of separate male and female reference ranges in this study, an evaluation of the possible sex dependency of plasma α fetoprotein concentration was attempted. Exponential and linear regression analyses were undertaken on age related α fetoprotein data segregated according to patient sex (Table 1). The almost identical values obtained for slope (−0·3695 for males versus −0·3761 for females) and ln [intercept] (23·4434 for males versus 23·6554 for females) parameters, derived from exponential regression of gestationally corrected α fetoprotein data for male and female infants, did not support the presence of a significant sex dependency. This was further confirmed by an even scatter of α fetoprotein results for boys and girls as shown in Figures 1 and 2.

Due to limited time and analytical resources it was impossible to gather the desired total of 20 plasma α fetoprotein values for each week of life from birth to 6 months hoped for at the outset of this study. No further action was taken to correct this disappointing shortfall in weekly age group totals. We had decided earlier that, for ethical reasons, the study infants would not be exposed to additional nonessential blood sampling simply to supplement incomplete age group quotas. Furthermore, the main incentive for this update of plasma α fetoprotein reference ranges was to improve diagnostic procedures for ill preterm and term infants admitted to neonatal surgical or medical units. It seemed inappropriate, therefore, to collect supplementary blood samples from 'well' baby populations, particularly when relevant but limited data could be gathered in the course of essential patient care. Thus α fetoprotein values were arranged almost entirely in age related groups of two weeks. Some small age related data sets with fewer than five plasma α fetoprotein values, although unusable for subsequent reference range computation, were retained for scattergram plotting in Figures 1 and 2.

Major anomalies were revealed during the first statistical analysis of age related α fetoprotein values, indicating that data were not disturbed in Gaussian form. With a range of five orders of magnitude, many individual values remained inexplicably outwith published plasma α fetoprotein reference ranges[14] and highlighted the need to establish revised ranges that took account of prematurity. These initial findings confirmed our earlier misgivings on the suitability of normal theory statistical analyses applied to unmodified plasma α fetoprotein frequency distributions.

Immediate improvement in distribution parameters was obtained by statistical evaluation of

Table 1 *Least squares regression of plasma α fetoprotein (U/ml) concentration versus patient age (weeks)*

	n	*Linear regression (Y=mX+c)*		*Exponential regression (ln(Y)=mX+ln(c))*	
		Correlation coefficient r	*p Value*	*Correlation coefficient r*	*p Value*
Uncorrected age:					
All patients	97	−0·42	<0·01	−0·85	<0·01
Male infants	54	−0·38	<0·01	−0·82	<0·01
Female infants	43	−0·48	<0·01	−0·91	<0·01
Corrected age:*					
All patients	94	−0·58	<0·01	−0·85	<0·01
Male infants	54	−0·55	<0·01	−0·81	<0·01
Female infants	40	−0·67	<0·01	−0·90	<0·01

*Definition of correction:

Corrected age (weeks) for preterm infants=Chronological age (weeks) at time of blood sampling minus gestational age deficit (weeks).

Gestational age deficit=Number of weeks preterm at birth (term=40 weeks)—for example, infant X with an estimated gestational age at birth of 28 weeks was 6 weeks old at the time blood was collected for α fetoprotein determination. Gestational age deficit=40–28—that is, 12 weeks. Corrected age (weeks)=6–12—that is, −6 weeks.

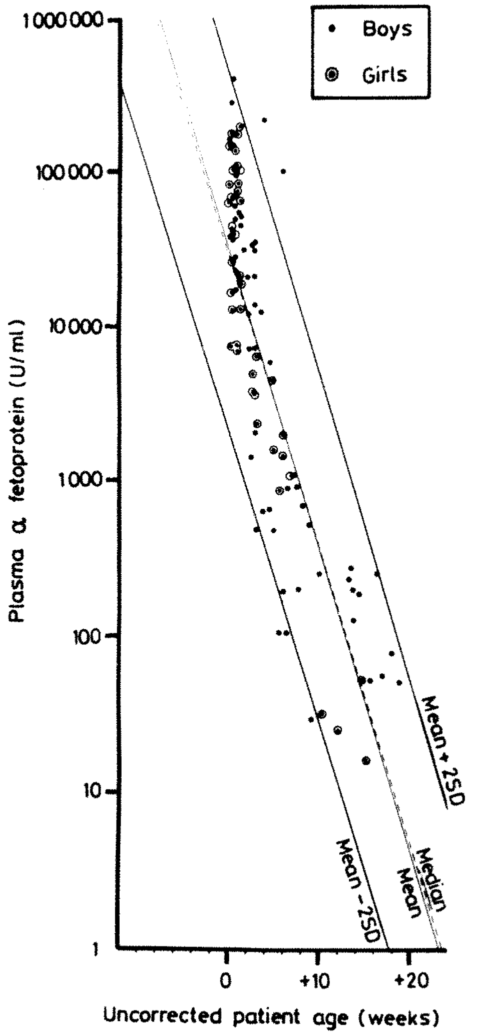

Fig. 1 *Plasma α fetoprotein results and Glasgow (Yorkhill) reference range for both preterm and term infants with no correction for gestational age deficit.*

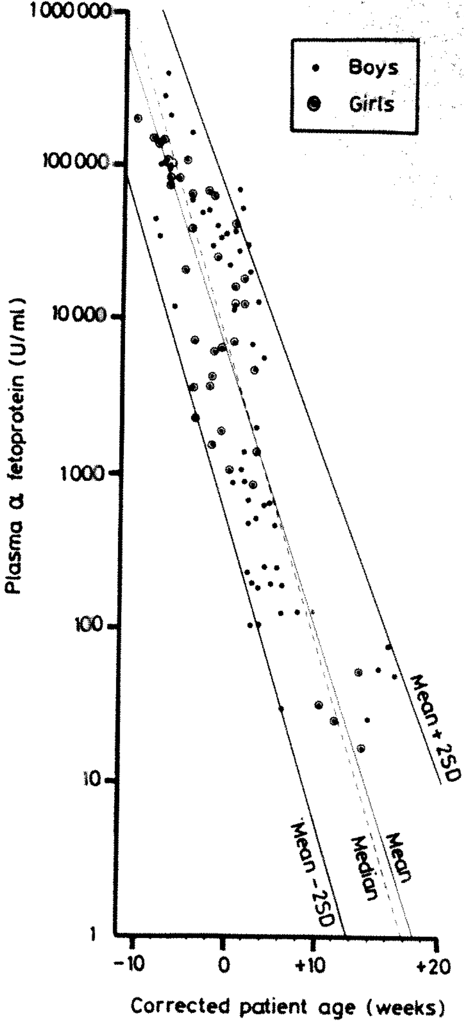

Fig. 2 *Plasma α fetoprotein results and Glasgow (Yorkhill) reference range for both preterm and term infants with correction for gestational age deficit.*

plasma α fetoprotein values ranked by patient age corrected for gestational age deficit (Table 2).

Previous work on maternal serum α fetoprotein reference ranges suggested that logarithmic transformation could be applied usefully to infant plasma α fetoprotein values.[16 20] The benefits of transformation were immediately evident from analysis of logarithmic α fetoprotein values versus uncorrected patient age with virtually coincident group means and medians and progressively decreasing lower (−2SD) limits, which were all above zero for the first time. Logarithmic transformation of plasma α fetoprotein data and ranking of $\log_e$α fetoprotein versus corrected patient age were combined in Table 3, on which the definitive plasma α fetoprotein reference ranges were based. Due mainly to the limited number of α fetoprotein results, the inconsistent values evident in Table 3 rendered it unsuitable for use as a table of reference ranges.

Unequivocal evidence for an exponential relation between plasma α fetoprotein concentration and infant age (regardless of prematurity) directed us to perform exponential least squares analyses on each column of derived data (lower/upper limits, mean, and median) versus respective mid-interval ages contained in Table 3. This latest statistical elabora-

Table 2 *Range of observed plasma α fetoprotein values ranked by patient age corrected for gestational age deficit at birth*

Corrected age interval (weeks)	*Mid-range point (weeks)*	*No of results*	*Male:female ratio*	*Lowest α fetoprotein result (U/ml)*	*Highest α fetoprotein result (U/ml)*
−10·0 – −8·1	−9·0	5	2:3	34572	196617
−8·0 – −6·1	−7·0	12	6:6	12012	391072
−6·0 – −4·1	−5·0	8	2:6	7293	161620
−4·0 – −2·1	−3·0	8	3:5	1549	67771
−2·0 – −0·1	−1·0	10	4:6	1932	40723
0·0 – 1·9	1·0	17	10:7	891	69720
2·0 – 3·9	3·0	16	13:3	105	20477
4·0 – 5·9	5·0	6	6:0	128	651
6·0 – 7·9	7·0	3	3:0	30	191
10·0 – 11·9	11·0	1	0:1	32	32
12·0 – 13·9	13·0	1	0:1	25	25
14·0 – 15·9	15·0	3	1:2	17	53
16·0 – 17·9	17·0	2	2:0	55	77
18·0 – 19·9	19·0	1	1:0	50	50

Table 3 *Plasma α fetoprotein ranked by patient age corrected for gestational age deficit at birth*

Corrected age interval (weeks)	*Mid-range point (weeks)*	*No of results*	*Derived from logarithmic α fetoprotein data transformation (U/ml)*			
			Mean	*Median*	*Mean −2SD*	*Mean +2SD*
−10·0 – −8·1	−9·0	5	90461	136106	18871	433644
−8·0 – −6·1	−7·0	12	105952	100897	19593	572936
−6·0 – −4·1	−5·0	8	44760	62135	4137	484258
−4·0 – −2·1	−3·0	8	13865	14864	893	215166
−2·0 – −0·1	−1·0	10	13641	23988	980	189915
0·0 – 1·9	1·0	17	9253	12777	411	208446
2·0 – 3·9	3·0	16	4167	766	45·9	29694
4·0 – 5·9	5·0	6	281	251	86·4	916

Table 4 *Plasma α fetoprotein reference ranges for preterm infants ranked by patient age uncorrected for gestational age deficit at birth*

Uncorrected postnatal age (weeks)	*Derived from exponential regressions of logarithmic α fetoprotein data (U/ml)*			
	Mean −2SD limit	*Mean +2SD limit*	*Mean*	*Median*
0	2146	473000	31864	29186
2	895	189300	13024	12208
4	374	75780	5323	5106
6	156	30330	2176	2136
8	65	12140	889	893
10	27	4860	363	374
12	11	1945	149	156
14	5	779	60·7	65·4
16	<4	312	24·8	27·3
18	<4	125	10·1	11·4
20	<4	50	4·1	4·8

tion provided the plasma α fetoprotein reference ranges in terms of unmodified infant age (Table 4) and of infant age adjusted for gestational age deficit (Table 5). Despite the presence of gaps related to a shortage of α fetoprotein data, visual corroboration of the validity of our entire statistical approach is clear from inspection of Figures 1 and 2 based on Tables 4 and 5. These show almost coincident mean and median regression lines with near parallel and equidistant lower (−2SD) and upper (+2SD) limit regression lines. The presence of some five α fetoprotein values out of a total of 93 collected from our ostensibly tumour free population sample, located at the margins of the mean (2SD) limits of

Table 5 *Plasma α fetoprotein reference ranges for preterm infants ranked by patient age corrected for gestational age deficit at birth*

Corrected postnatal age (weeks)	*Derived from exponential regressions of logarithmic α fetoprotein data (U/ml)*			
	Mean −2SD limit	*Mean +2SD limit*	*Mean*	*Median*
−10	38910	2034000	281298	410815
−8	15960	988900	125633	172801
−6	6548	480800	56109	72684
−4	2686	233800	25060	30573
−2	1102	113700	11192	12860
0	452	55270	4999	5409
2	185	26870	2232	2275
4	76	13070	997	957
6	31	6353	445	403
8	13	3089	199	169
10	5	1502	88·8	71·2
12	<4	730	39·7	30·0
14	<4	355	17·7	12·6
16	<4	173	7·9	5·3
18	<4	84	3·5	2·2
20	<4	41	1·6	0·9

Figure 2, is encouraging evidence that the theoretical characteristics of a normal distribution are present.

Discussion

Clinical interpretation of plasma α fetoprotein concentrations obtained during the first few weeks of life can be rendered difficult due to frequent misclassification of high plasma α fetoprotein concentrations observed in preterm infants. This study has determined a provisional range of plasma α fetoprotein reference values for ill term and preterm infants that, although sufficiently wide to enclose almost all results from the 'normal' subjects in this study, seemed to detect pathological increases in plasma α fetoprotein.

The predictive capability of these ranges was tested first with plasma α fetoprotein results collected from five infants (three term and two preterm) excluded at the outset of the data treatment due to the presence of sacrococcygeal teratoma, which, in retrospect, proved clinically and histologically benign. Serial plasma α fetoprotein results (mainly post-excision) from two preterm babies (with gestational ages of 31 and 32 weeks) with benign sacrococcygeal teratoma were plotted on Tsuchida's graph[14] (Fig. 3(a)). Several values were located either at or above the upper limit of the '95% prediction band' without discernible clinical cause. When the patient ages were adjusted for gestational age deficit and the same plasma AFP data replotted on our revised reference range graph (Fig. 3(b)) all α fetoprotein values for benign teratoma, including results for the three term infants, remained comfortably within mean (2SD) limits.

Due to the rare incidence of yolk sac derived and hepatic malignant tumours in early infancy, no plasma α fetoprotein results were available for evaluation during the study from babies with suspected or proven α fetoprotein producing tumours. None the less we attempted a minimal evaluation of the ranges in relation to malignancy by plotting serum α fetoprotein results obtained by radioimmunoassay from two published cases of malignant tumour in infancy (pre-resection hepatoblastoma and post-resection orchioblastoma).[13] Both serum α fetoprotein values were located well above the (+2SD) upper limit (Figure 3(b)).

Assessment of the diagnostic potential of our α fetoprotein ranges in relation to non-malignant paediatric liver disease was impossible without resorting to previously published α fetoprotein data, there being no established cases in the group studied. Maximal serum α fetoprotein results collected by Zeltzer *et al* from 19 term infants with an established diagnosis of biliary atresia or hepatitis[6] were plotted on the graph (Figure 3(b)). Results of this retrospective comparison plot tended to suggest that earlier biochemical differentiation between neonatal hepatitis and biliary atresia may be realised by plasma α fetoprotein monitoring, although not without further study. Clearly, these preliminary findings must be treated with caution in view of the substantial methodological differences between Zeltzer's radial immunodiffusion technique and modern α fetoprotein radioimmunoassays and perhaps more importantly the assumed patient ages at sampling.

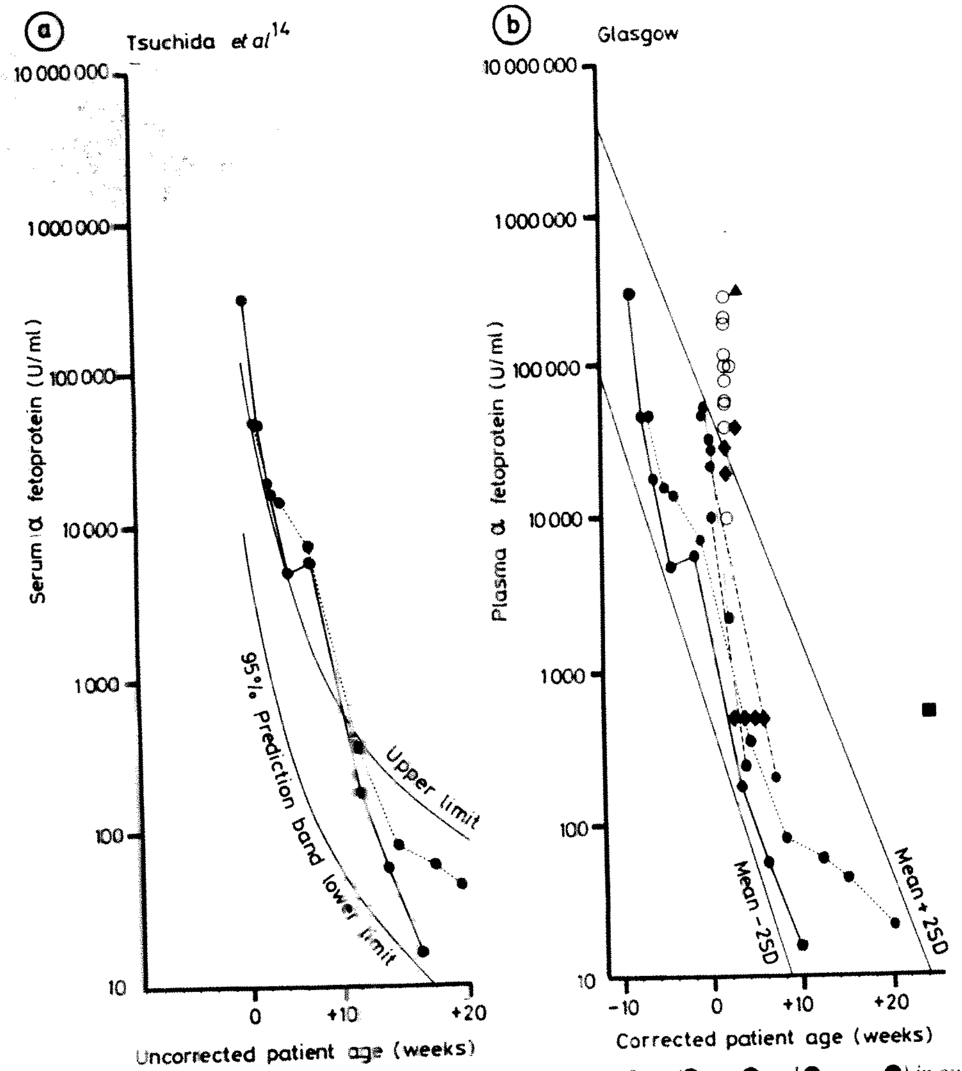

Fig. 3(a) *Serial plasma α fetoprotein results from two preterm infants (●——● and ●- - -●) in our study with benign sacrococcygeal teratoma plotted on the reference range graph of Tsuchida* et al.[14] *(b) Serial plasma α fetoprotein results from two preterm and three term infants (represented by black dots) in our study with benign sacrococcygeal teratoma plotted on the Glasgow (Yorkhill) reference range graph together with serum α fetoprotein data from two published cases of malignant tumour in infancy (pre-resection hepatoblastoma (▲) and post-resection orchioblastoma (■)[13]) and maximal serum α fetoprotein results published for 19 term infants with biliary atresia (◆) or hepatitis (○).*[6]

In conclusion, we have shown, despite the limited data available, the relative simplicity of deriving paediatric reference ranges for plasma α fetoprotein with the aid of gestational deficit adjustment and a single step data transformation. Our findings may encourage others to derive similar laboratory reference ranges for plasma α fetoprotein based on paediatric results obtained by local assay methods and thereby confirm or refute the value of plasma α fetoprotein as a marker for non-malignant disease in early infancy.

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British Paediatric Association

Annual meetings

At York University:
1987 April 7–10
1988 April 12–16
1989 April 11–15

At University of Warwick:
1990 April 3–7
1991 April 16–20
1992 April 7–11
1993 April 19–23 (provisional)
1994 April 11–15 (provisional)

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Screening for late neonatal vitamin K deficiency by acarboxyprothrombin in dried blood spots

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SUMMARY Acarboxyprothrombin (protein induced by vitamin K absence or antagonist-II (PIVKA-II)) concentrations in dried blood spots were determined in 19 029 infants at about 1 month of age as an indicator of vitamin K deficiency. We observed 51 cases with raised blood concentrations of PIVKA-II (>4 AU/ml), nine of whom showed very high concentrations (>20 AU/ml).

For infants who did not receive vitamin K prophylaxis at birth, the incidence of the PIVKA-II test yielding positive results was significantly higher in those solely breast fed (0·51%) compared with those fed formula milk (0·18%). Among solely breast fed infants, the incidence of a very high result of the PIVKA-II test was 0·14% in those who had not received vitamin K prophylaxis at birth, 0·04% in those who received 2 mg orally, and 0·03% in those who received 2 mg orally plus a further dose of 2–4 mg orally at 7 days.

Thus vitamin K prophylaxis at birth did not completely prevent vitamin K deficiency at 1 month. We administered vitamin K therapeutically to all infants whose PIVKA-II test yielded a positive result at 1 month. Only one infant with a positive result developed late neonatal intracranial haemorrhage.

Severe intracranial haemorrhage related to vitamin K deficiency in infants aged 1 month may occur suddenly and lead to death or severe central nervous system dysfunction. Almost all of the affected infants who have been reported had not received vitamin K at birth.[1-8] The American Academy of Pediatrics recommends that all newborn infants receive vitamin K (a single parenteral dose of 0·5–1·0 mg or 1·0–2·0 mg orally).[9] In Japan newborn infants are not given routine vitamin K prophylaxis. This might be one of the reasons for the high incidence of late neonatal vitamin K dependent intracranial haemorrhage in our country. This disorder occurs in one in every 4500 infants and one in every 1700 breast fed infants who are not given vitamin K prophylaxis.[1]

Recently, the study group of the Ministry of Health and Welfare of Japan recommended that all newborn infants should receive vitamin K orally,[1] but intramuscular administration of the vitamin was not recommended. In this study we report a mass screening system for acarboxyprothrombin (protein induced by vitamin K absence or antagonist-II (PIVKA-II)) as an indicator of vitamin K deficiency at 1 month. PIVKA-II is a precursor of active prothrombin and converted to the active form by vitamin K and carboxylase.[10] This study aimed to evaluate the effect of oral vitamin K that had been administered after birth and to detect patients with severe vitamin K deficiency at 1 month before symptoms occurred.

Patients and methods

Plasma PIVKA-II concentration was measured by means of an assay using a monoclonal, monospecific antibody.[11] The PIVKA-II concentration in dried blood spots was determined as follows. Blood was spotted on filter paper, four discs of 6 mm diameter were punched out for each individual, and then the blood was eluted from the discs for one hour in 0·3 ml of phosphate buffered saline (10 mM phosphate buffer and 150 mM sodium chloride, pH 7·4), with horizontal shaking. Then 100 μl of the eluate was subjected to the PIVKA-II assay as described previously.[11] Each measurement was performed in duplicate. The PIVKA-II concentrations determined for the same blood sample with different assay systems were compared to evaluate the reliability of the dried blood assay system.

Monitoring of PIVKA-II concentrations by the blood spot test was carried out in 19 029 young infants aged about 1 month in the Kumamoto region of Japan between April 1984 and January 1986. Measurements were made within 24 hours of receiving the samples. Roughly 90% of the breast fed infants in this area were included in this survey. The infants consisted of 11 107 who were breast fed, 7157 who were both breast and formula fed (mixed fed), and 765 who were formula fed. As breast feeding is known to be a risk factor for vitamin K deficiency most of the women who participated in the monitoring were breast feeding their infants. The incidence of haemorrhagic disease in the first week of life among these infants was not known and infants who showed early neonatal bleeding were not excluded. Those infants allocated to receive vitamin K were given either 2·0 mg orally within 24 hours of birth (one dose) or this initial dose plus 2–4 mg orally at 1 week of age (two doses). The decision to administer vitamin K and the manner of administration were determined by the obstetricians. The vitamin was given as vitamin K_2 syrup (Kay Two Syrup (menaquinone 4, 2-methyl-3-all-trans-tetraprenyl-l, 4-maphthoquinone), Eisai Co Ltd, Tokyo, Japan) because vitamin K_1 was unavailable as a syrup in Japan.

In Japan all infants are examined under the child health survey program at 1 month of age. At this examination we obtained informed consent from all the parents and then took blood samples from the infants by means of a heel puncture, which were then spotted onto filter paper, dried, and sent to our laboratory by post.

The cut off point for PIVKA-II on the blood spot test was set at 4·0 AU/ml. One arbitrary unit (AU) corresponds to 1 μg purified prothrombin. Our preliminary study suggested that in breast fed infants aged 1 month who had not received vitamin K prophylaxis the 0·6 centile for PIVKA-II might be about 4·0 AU/ml.[12] This cut off point was anticipated to select 10-fold the number of infants with late onset bleeding due to vitamin K deficiency, based on an estimated incidence of 0·06%.[1] When the result was above this the plasma PIVKA-II concentration and normotest activity were measured by methods previously described[11] and then 5 mg vitamin K_2 given orally.

When the PIVKA-II concentration was higher than 20 AU/ml according to the blood spot test 1–2 mg vitamin K_2 was injected within six hours of the diagnosis being made. Infants with normotest activities of under 20% had a computed tomogram taken. The normotest activity reflects the total coagulant activities of factors II, VII, and X.[13] The normal mean (SD) normotest value in breast fed infants at 1 month of age is 71·4 (17·0)% (n=218).[14]

The comparison of incidences between various groups was analysed by the χ^2 test with Yates's correction.

Results

Measurement of PIVKA-II in dried blood spots. Figure 1 shows the correlation between PIVKA-II values on dried blood spots and those obtained by measuring PIVKA-II in plasma samples from the same subjects. Blood samples with high PIVKA-II concentrations were obtained from 27 adults receiving warfarin as it was difficult to obtain many samples from the infants with vitamin K deficiency at the same time. The high correlation indicated that the dried blood method was reliable for measurement of PIVKA-II concentrations. The detection limit for blood PIVKA-II was 1·0–32·0 AU/ml with the dried blood method. The coefficients of variance of intra- and interassays were less than 0·06. The recovery of PIVKA-II from dried blood spots was monitored after spotting. A mean of 87·7% (n=27) of the initial PIVKA-II concentration was found at room temperature on the fifth day after the blood had been obtained.

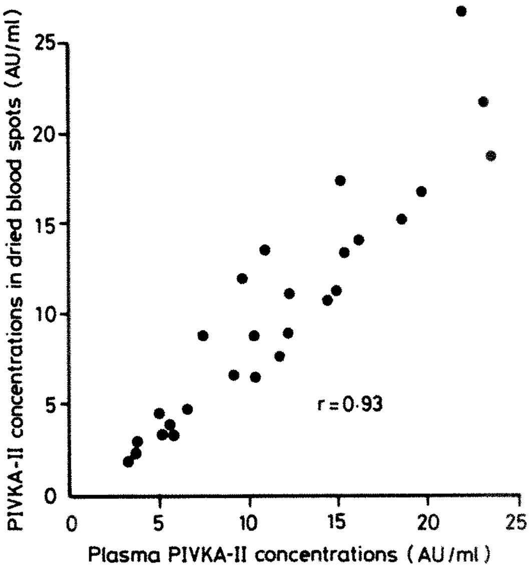

Fig. 1 *Correlation between PIVKA-II concentrations in dried blood spots and in plasma samples from the same subjects. The equations for the regression lines for the PIVKA-II values for dried spots* v *those for plasma are* $y=0\cdot97x-1\cdot07$, $r=0\cdot93$, $p<0\cdot005$.

Table 1 *Infants with positive results of PIVKA-II test according to method of feeding and vitamin K prophylaxis at birth*

Group	Vitamin K prophylaxis	No	PIVKA-II >4AU/ml (No (%))†		PIVKA-II >20 AU/ml (No (%))†	
			Solely breast fed	Mixed or formula fed	Solely breast fed	Mixed or formula fed
1	None	8346 (5090)*	26 (0·51)	6 (0·18)	7 (0·14)	0 (0)
2	2 mg orally on day 1	5169 (2811)*	10 (0·36)	3 (0·13)	1 (0·04)	0 (0)
3	2 mg orally on day 1 and 2–4 mg on day 7	5514 (3206)*	6 (0·19)	0 (0)	1 (0·03)	0 (0)
	Total	19 029	42 (0·38)	9 (0·11)	9 (0·08)	0 (0)

*No of solely breast fed infants.
†AU=Arbitary unit.
PIVKA-II >4 AU/ml=Group 1 *v* group 3, $p<0{\cdot}01$; group 1 *v* group 2, not significant; group 1 solely breast fed *v* group 1 mixed or formula fed, $p<0{\cdot}05$; total solely breast fed *v* total mixed or formula fed, $p<0{\cdot}01$
PIVKA-II >20 AU/ml: Total solely breast fed *v* total mixed or formula fed, $p<0{\cdot}05$.

Table 2 *Clinical and laboratory data of infants with very high PIVKA-II concentrations (>20 AU/ml)*

Case no	Age (days)	Sex	PIVKA-II concentrations		Normotest activity (%)
			Dried blood	Plasma	
1	31	M	>32·0	40·1	<10
2	32	M	>32·0	54·4	<10
3	36	F	>32·0	65·5	<10
4	39	M	>32·0	ND	ND
5	31	M	>32·0	ND	ND
6	33	M	>32·0	38·0	<10
7	31	F	>32·0	54·4	11·0
8	37	M	>32·0	69·7	12·5
9	35	M	16·7	23·24	15·0

ND=Not done.
All but case 9 had blood spot values above the upper detection limit (>32·0 AU/ml). Case 9 was included because plasma PIVKA-II was above 20 AU/ml.

Results of screening for vitamin K deficiency. The results of the screening survey are shown in Table 1. Fifty one cases with high PIVKA-II concentrations (>4·0 AU/ml) were found among the 19 029 infants who were monitored. Of these, 42 were solely breast fed, nine mixed fed, and none solely formula fed.

For infants who did not receive vitamin K prophylaxis, the incidence of vitamin K deficiency was higher in those who were entirely breast fed compared with those who received formula or mixed feeds ($p<0{\cdot}05$). When all the infants were classified into three groups according to vitamin K prophylaxis—group 1 (none), group 2 (2 mg orally at birth), and group 3 (2 mg orally at birth and 2–4 mg orally at 1 week)—the incidence of vitamin K deficiency was higher in group 1 (32 of 8346, 0·38%) compared with group 3 (6 of 5514, 0·11%) ($p<0{\cdot}01$).

All nine cases of severe vitamin K deficiency (PIVKA-II >20 AU/ml) were entirely breast fed. Seven belonged to group 1 for vitamin K prophylaxis and one to each of the other two groups. Although the incidence of severe vitamin K deficiency did not differ significantly between these groups, there was a trend towards a decreasing incidence of severe vitamin K deficiency with increasing vitamin K prophylaxis (from group 1 to group 3) (Table 1).

Clinical and laboratory data. Laboratory data for the nine infants with severe vitamin K deficiency are shown in Table 2. After the intramuscular injection of 1–2 mg vitamin K normotest activities returned to normal within 24 hours and plasma PIVKA-II concentrations decreased gradually and reached normal within eight to 14 days (Fig. 2).

Only one of the 51 infants with a positive result of the PIVKA-II test had evidence of late onset haemorrhage, and that was a baby with severe vitamin K deficiency who had an asymptomatic small subdural haemorrhage apparent on computed tomography (Table 2, case 2). Among the other infants with severe vitamin K deficiency, a diagnosis of congenital bile duct atresia was later established in case 6. Other forms of hepatic dysfunction, manifest by raised serum transaminase activities, were observed in cases 2 and 4.

In the present study only one infant with a negative result of the PIVKA-II test had late onset haemorrhage (intracranial bleeding), and this occurred 21 days after the blood spot test had yielded negative results. This infant had congenital bile duct atresia.

Discussion

Direct determination of plasma vitamin K may lead to a greater understanding of the role of this vitamin,[15] but the direct assay is not practical for a

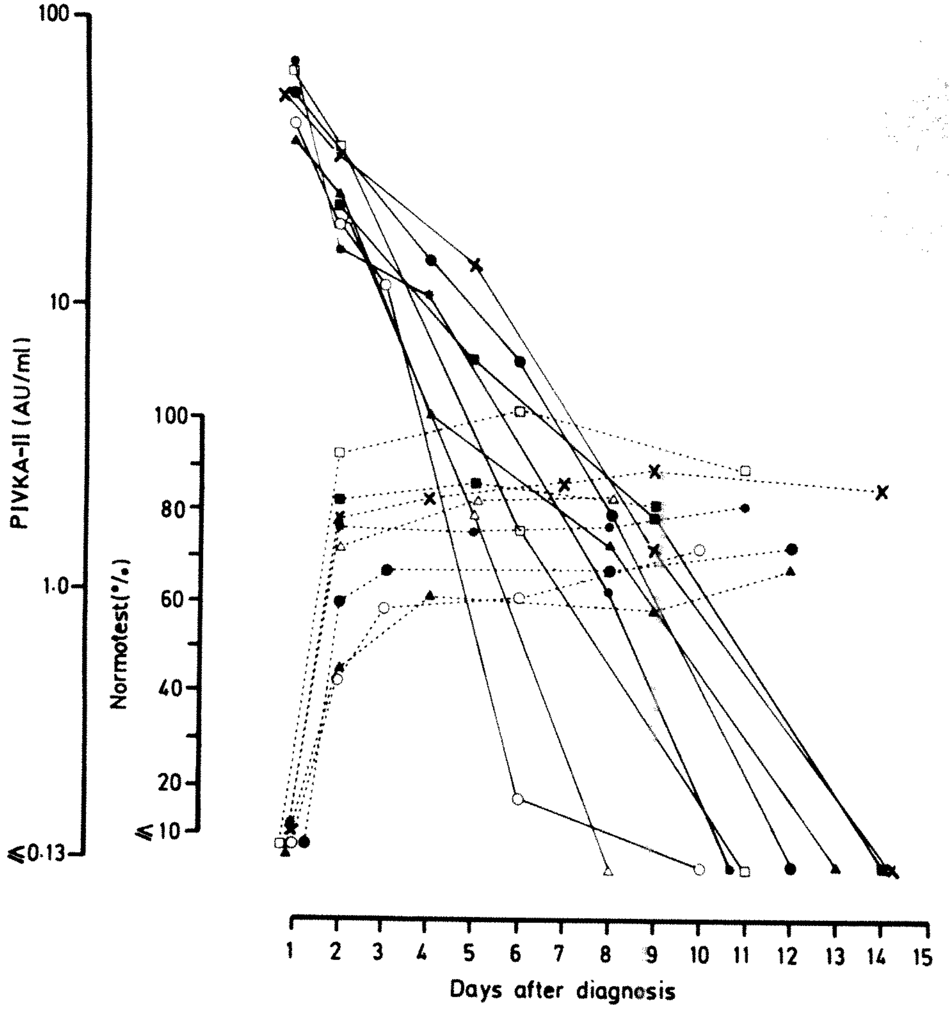

Fig. 2 *Effects of intramuscular administration of vitamin K_2 (1–2 mg) on plasma PIVKA-II and normotest activity in infants with vitamin K deficiency. The solid lines represent plasma PIVKA-II, the broken lines the normotest activity. The eight infants represented here are those with blood spot PIVKA-II concentrations >20 AU/ml. All had values above the upper limit of detection (>32 AU/ml).*

hospital service. PIVKA-II occurs in peripheral blood in vitamin K deficiency or patients treated with warfarin but is not present in normal adults.[10 16–18] Thus measurement of the plasma PIVKA-II concentration is useful for evaluating vitamin K deficiency. Previously, we measured PIVKA-II concentrations in newborn infants as an indicator of vitamin K deficiency and concluded that oral vitamin K prophylaxis at birth was effective in preventing early neonatal bleeding.[19]

Faced with the need for prophylaxis for all neonatal infants, physicians have been reluctant to use the usual intramuscular injection routinely in Japan. McNinch *et al* and Sann *et al* reported that serum vitamin K concentration increased considerably after oral administration of vitamin K (1–2 mg) and concluded that oral administration of vitamin K was sufficient to prevent neonatal bleeding due to vitamin K deficiency.[20 21] Oral prophylaxis with vitamin K in newborn infants is more economical and simpler than intramuscular prophylaxis. The oral route is most practical when routine administration is required for all newborn infants.

It is not clear at present whether oral administration of vitamin K in the neonatal period is effective in preventing late onset infantile bleeding due to vitamin K deficiency at about 1 month of age.[22] We have been unable to find any published data relating to this problem. The purpose of this survey was to obtain both a scientific basis for an effective protocol for preventing vitamin K deficiency and a means of identifying this disease before clinical symptoms occurred. To achieve this a large number of subjects was necessary as the incidence of the disease is fairly low. We therefore developed the mass monitoring system for PIVKA-II described in this paper. The reliability of the simplified method using dried blood spots was sufficient for these purposes.

In this study the infants were divided into three groups according to vitamin K prophylaxis. We could then evaluate the prolonged effect of administration of vitamin K in the newborn period. We showed that breast feeding was a risk factor for the disease, supporting the results of retrospective surveys.[1-8] The incidence of infants with a PIVKA-II test that yielded positive results (>4 AU/ml) among untreated infants was higher compared with those given two doses of vitamin K, whereas the incidences of very high PIVKA-II concentrations (>20 AU/ml) in the two treated groups were similar. We are unable to conclude at present whether or not a double dose of vitamin K offers more protection than a single dose. It was hoped that both neonatal bleeding and late onset infantile bleeding could be prevented with a single administration of vitamin K at birth. Our results, however, suggested that vitamin K prophylaxis once or twice at birth was not sufficient completely to prevent vitamin K deficiency at 1 month.

We found 51 cases of vitamin K deficiency, nine of whom had very high concentrations of PIVKA-II on the blood spot test or plasma assay. Seven of these cases had critically low clotting activity based on the normotest. Of the nine cases with severe vitamin K deficiency, one had congenital bile duct atresia and two mildly raised serum transaminase activities, whereas the remaining six cases had no predisposing factors such as chronic diarrhoea, malnutrition, or broad range antibiotics. Vitamin K dependent coagulant activities promptly improved and the plasma PIVKA-II concentration decreased gradually in all cases on an injection of vitamin K. Only one of these cases had intracranial haemorrhage. It can be speculated that the monitoring system and treatment was effective.

Over three years (1979–81) 16 cases of late onset vitamin K deficiency were reported in the area where this study was performed[14] and almost all these infants did not receive vitamin K prophylaxis. During the period of this study (21 months), based in the same area, only three cases of vitamin K deficiency were observed. In one of these cases the deficiency occurred at 28 days of age—that is, before the PIVKA-II concentration was measured—and was therefore not included in this report. The others were case 2 in Table 2 and the case of congenital bile duct atresia mentioned above.

A recent survey by the study group of the Ministry of Health and Walfare of Japan indicated an incidence of three in 1000 infants with critical normotest activities (below 20%) for 1 month old breast fed infants who did not receive vitamin K prophylaxis. The study group speculated that one in four or five infants with normotest values <20% might develop a bleeding disorder due to vitamin K deficiency as the incidence of the disease was 1 in 1700 in breast fed infants.[1] The incidence of critical normotest activities is close to the incidence of infants with high PIVKA-II concentrations (above 20 AU/ml).

We speculate that some infants with high PIVKA-II concentrations might have suffered from the disease if they had not received vitamin K. The decrease in the number of patients seemed to be due to the prophylactic administration of vitamin K, which was performed for roughly 60% of the infants in this area, or the selective administration of vitamin K to infants with high PIVKA-II concentrations found by screening, or both.

Because screening for vitamin K deficiency by means of this method costs much more than the routine administration of vitamin K, both economically and socially, we hope to prevent the disease by means of prophylactic administration of the vitamin to all newborn babies. If the oral administration of vitamin K is continued as a routine method of preventing the disease the optimal dose of the vitamin needs to be determined.

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A simple method of face mask resuscitation at birth

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SUMMARY Twenty two infants were resuscitated at birth using a face mask connected to an oxygen supply from a conventional resuscitaire. Intermittent finger occlusion provided the positive pressure within the mask. This method was apparently at least as effective as the best bag and mask systems and was convenient to use.

Resuscitation of infants using a bag and face mask is a well accepted technique and seems empirically to be successful. The essential features to obtain the best results are a round mask, with a compliant ring to form an adequate seal,[1] a large reservoir to allow a more sustained pressure[2] with a robust design, and sufficient staff training. Even so the results of Milner *et al* showed that compared with intubation face mask resuscitation rarely produced volumes adequate for alveolar ventilation and worked mainly by stimulating the baby's own respiratory efforts.[3] Theoretically, face mask resuscitation is attractive as it is safe, it is easy to learn, and fears about gastric distension have proven groundless.[4] Studies on intubated babies have shown, however, that tidal exchange can be improved further if the initial inflation pressure can be maintained for at least two seconds.[5] To achieve this we have mounted the oxygen supply of a conventional resuscitaire into a face mask so that the inflation pressure can be provided by occluding the flow out of the mask. This allows easy control of the duration of inflation and is less cumbersome.

Methods

Elective and emergency caesarean sections of term babies were attended. Resuscitation was begun if the Apgar score was less than 6 and was associated with apnoea. The Figure shows a diagram of the apparatus. A standard round padded face mask (Ambu) was used with two small holes drilled in the hard perspex portion. One was attached to a pressure transducer (Bell and Howell) to measure the mask pressure, and the other provided a bias flow of air from the resuscitaire with a pressure blow off valve. The set pressure was varied to provide a range of mask pressures up to 30 cm H_2O. A mercury pneumotachograph was attached to the central hole in the face mask and connected to a differential pressure transducer (SE Labs) to measure expiratory flow. Both pressure and flow signals were amplified and displayed on a two channel Devices pen recorder. Volume was calculated from the area under the flow curve. Positive pressure was provided by occluding the end of the pneumotachograph with a finger. The mask was held firmly to the baby's face and the first inflation was prolonged (2–5 seconds) with subsequent inflations of 0·5–1 seconds at a rate of 30–60 per minute—that is, standard resuscitation procedure. Resuscitation was then continued as indicated clinically.

Subjects

Data were obtained from 22 full term infants delivered by caesarean section. Eleven of the 22 were boys, and the mean gestational age was 39 weeks (range 37–41 weeks) and mean birth weight 3280 g (range 1800–4300 g). Most of the babies made an initial cry before an episode of apnoea, but

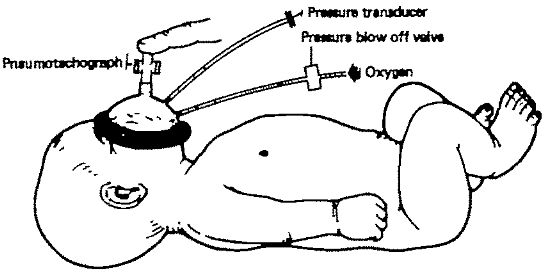

Figure *Mask resuscitation and monitoring apparatus. Pressure is applied by occluding the flow outlet of the mask with a finger.*

in four cases there were no respiratory efforts before resuscitation. Eighteen were elective sections, the principal indications being breech presentation (six cases) cephalopelvic disproportion/previous section (six), and placenta praevia (two)). The four emergency sections—that is, performed after the start of the first stage of labour—were for fetal distress (three cases) or failure to progress in labour (one). All the babies studied were normal at the postnatal examination at 24 hours.

Results

All the babies were successfully resuscitated using this system, except one who required intubation and ventilation for two minutes. This baby had been delivered electively at 39 weeks because of breech presentation At birth the baby was clinically asphyxiated with an Apgar score of 1. Face mask resuscitation was started, but the heart rate remained between 50–100 beats/min and a clinical decision was made to intubate. After intubation the heart rate quickly improved and the subsequent course was uneventful. Subsequent analysis showed that all the expiratory volumes were less than the respiratory dead space.

The anatomical dead space of the respiratory system is 2·2 ml/kg and is independent of age [6] We defined adequate ventilation as being 4·4 ml/kg or more—that is, two dead spaces—implying some degree of alveolar ventilation. The proportion of babies needing more than three inflations before onset of spontaneous breathing was small, so the first three inflations were analysed (Table 1). With each inflation 22–32% of the babies achieved an adequate expiratory volume (≥ two dead spaces). If this is compared with the best bag and mask systems from a previous study using the same recording equipment[3] the efficacy is similar (Table 2). As a result of the variation in the blow off pressure, however, mean pressure generated was less than with the bag and mask systems. There was a significant relation between adequate expiratory volume and pressure generated in the mask ($z=4\cdot51$, $p<0\cdot001$, Wilcoxon two sample test), suggesting that the lower pressures used in this study were too low for optimal tidal exchange This is borne out by the significant increase in adequate expiratory volume with pressures above 25 cm H_2O to the extent that the success rate was 54% above this pressure and 10% below it (Table 3).

Table 1 *Expiratory volumes from the first three inflations during resuscitation*

	Inflation			
	First	*Second*	*Third*	*All three*
No of patients	22	22	21	65
Inflation pressure (cm H_2O) (Mean (range))	27 5 (20–34)	23 3 (12–32)	23 5 (15–30)	24 4
Expiratory volume (No of dead spaces)				
<1	10	12	12	34
1	5	4	4	13
≥2	7	6	5	18

Table 2 *Comparison of bag and mask resuscitation systems with the present study*

	Present study	*Other systems*	
		*Ambu**	*Laerdal** *(paediatric)*
Mean inflation pressure (cm H_2O)	24 4	26 9	30 3
No (%) of inflations achieving adequate ventilation	18/65 (28)	12/30 (40)	6/30 (20)
No (%) of babies with at least one adquate volume in first three inflations	8/22 (36)	4/10 (40)	3/10 (30)

*Results taken from Field *et al* [2]

Table 3 *Relation between inflation pressure ≥25 cm H_2O and adequacy (≥4·4 ml/kg) of tidal volume*

	Expiratory volume		*Total*
	Adequate (≥4 4 ml/kg)	*Less than adequate (<4 4 ml/kg)*	
Inflation pressure			
≥25 cm H_2O	14	12	26
<25 cm H_2O	4	35	39
Total	18	47	65

$\chi^2=12\ 7$, $p<0\ 001$

The effect of the babies' own respiratory efforts was also examined. In 14 of the 65 inflations the baby made an inspiratory effort, and eight of these were associated with an adequate expiratory volume This association was significant ($\chi^2=5\cdot97$, $p<0\cdot02$) There was also an association between the presence of an inspiratory effort and the mask pressure ($z=2\cdot52$, $p<0\cdot01$, Wilcoxon two sample test), but not enough to explain all the influence of pressure on adequate volume.

Discussion

At birth a baby's airways are full of fluid. As tidal ventilation begins some of the inspired gas may form an initial functional residual capacity. In this situation inspiratory volume will be larger than expiratory volume. As a result of inevitable leak around the face mask on inflation, it was not possible to measure inspiratory volumes so the expiratory volumes presented here may underestimate the gas available for respiration. Babies born by caesarean section, however, are much less likely to form a functional residual capacity after the first breath than those delivered vaginally,[7] and we think this is unlikely to alter our results appreciably.

The pressure applied to the airways depends on the blow off valve, the seal of the mask around the face, and the flow of gas. In view of the correlation between pressure and adequate volume the results with this technique could be improved with consistent inflation pressures of more than 25 cm H_2O. From a practical point of view this method of resuscitation was found to be convenient and easy to use and it was possible to hold the mask to the baby's face and apply the inflation pressure with one hand, leaving the other free. In units with a resuscitaire it is a cheap, convenient, and effective way of providing a face mask facility.

We are grateful to The Medical Research Council for fundi this project

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Trends in birth prevalence of cerebral palsy

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SUMMARY A register of children with cerebral palsy born in the period 1966–77 to mothers resident in the Mersey region was compiled from several different data sources. There were 685 cases, with a male:female ratio of 1·4:1. The birth prevalence of cerebral palsy ranged from 1·18 to 1·97 per 1000 live births each year, with a mean of 1·51 per 1000 live births. There was no discernible trend in overall prevalence, but there was a highly significant upward trend in the prevalence of cerebral palsy among low birthweight infants, which was evident for all the major types of cerebral palsy. It is postulated that this is due to improved survival rather than a real change in incidence. Alternatively, because the register was compiled from health service records, a diagnostic access bias from improved follow up of low birthweight infants may have led to an apparent increase in prevalence.

Cerebral palsy has been defined as comprising 'a group of disorders of movement and posture due to a defect or lesion of the immature brain'.[1] In recent years there has been mounting interest in cerebral palsy, particularly in possibilities for its prevention. In part this interest has been precipitated by the improvement in survival in low birthweight infants, which has paralleled the development of special and intensive care nurseries.[2 3] In Little's classic description over a century ago the common association of premature birth with cerebral palsy was recognised.[4] While modern neonatal intensive care has been in the forefront of medical advance and is associated with improved survival, there is still speculation that the improvement may only be at the cost of an increase in prevalence of cerebral palsy and other disabilities.[5–7] It is for this reason that the monitoring of cerebral palsy epidemiology in conjunction with mortality statistics has been suggested as an indicator of the gains and hazards of perinatal care.[8]

Recent studies examining birthweight specific trends in the prevalence of cerebral palsy have shown conflicting trends In Sweden there was a fall in the overall trend between 1954 and 1970 from 2·2 to 1·3 per 1000 live births, due mainly to a decrease in the syndromes of spastic and ataxic diplegia, particularly among low birthweight babies and in the group with perinatal causes of cerebral palsy.[9] Subsequently, however, there was an increase in prevalence to 2·0 per 1000 in the period 1975–78, which was mainly due to spastic/ataxic diplegias among preterm infants.[10] The series from Western Australia covered the period 1956–75; the observations differed in two important respects from the Swedish study. There was a significant rise in the prevalence in the 1966–70 period followed by a highly significant fall in the 1971–75 period, which was of equal magnitude in infants of low (≤2500 g) and normal (>2500 g) weight at birth.[11] The most recent study from the north east of England, covering the period 1960–75, found a decrease in prevalence among very low birthweight babies but an increase among babies weighing more than 2500 g at birth.[12]

We report here an examination of the trends in the birthweight specific prevalence of cerebral palsy at birth in the Mersey region from 1966 to 1977.

Patients and methods

A register was compiled of all cases of cerebral palsy born in the years 1966–77 whose mother's area of residence at the time of birth was within the boundary of the Mersey Regional Health Authority. The 1974 National Health Service and Local Authority reorganisation was associated with the redrawing of geographical boundaries. Before 1974, those county councils and boroughs and urban and rural districts that subsequently constituted the Mersey region after the 1974 reorganisation provided the geographical delineation of the study area. As the mother's area of residence at the time of birth was the criterion for inclusion infants born within the region but whose mother's area of residence was outside were excluded; those born outside but whose mother's area of residence was within the region were included. These inclusion and exclusion criteria were applied because denominator data for live births obtained from birth registration procedures are published according to the mother's area of residence at the time of birth.

To ensure completeness of ascertainment of cases, several sources of information were used. Handicap registers in each of the 10 health districts in the region were abstracted for all cases with a diagnosis of cerebral palsy or possible cerebral palsy In addition, a list of all cases of the disease resident in the Mersey region was obtained from the national register of families claiming a family disability allowance, which is maintained by the Rowntree Trust at York. Records of all children attending schools for the educationally subnormal (moderate and severe) and the physically handicapped were inspected and any child with a diagnosis of cerebral palsy was noted. Lastly, through the Office of Population Censuses and Surveys (OPCS), a search was made for all death certificates in which the disease featured as the underlying cause of death on Part I or as other significant condition contributing to the death on Part II of the certificate.

The categorisation of type of cerebral palsy was made on the basis of information in the clinical records of each child The records of all doubtful cases were reviewed by one of us (LR). A case was classified as 'acquired' if the presumed insult to the brain occurred after the 28th day of life. If there was uncertainty about the timing of the insult the aetiology was presumed congenital All acquired cases were excluded from subsequent analysis Cases with symmetrical or nearly symmetrical spasticity of the legs with lesser involvement of either arm were designated as having spastic diplegia Cases with unilateral spasticity of one arm and one leg were designated as hemiplegia and those with arms and legs equally affected or with deficits greater in the arms than the legs as spastic quadriplegia. If, in addition to the spasticity, dyskinesia or ataxia was present the child was labelled as a 'mixed' case The remaining cases designated 'other' included the athetoid, ataxic, and dystonic forms.

Denominator data for determining birth prevalences of cerebral palsy were obtained from the Registrar General's and OPCS tables of birth registration. Grouped birthweight specific data for infants weighing 2500 g or less were obtained from the LHS 27/1 returns compiled by the Department of Health and Social Security (DHSS) from birth notifications. Numbers of live births of infants weighing over 2500 g were obtained by subtracting birth *notifications* 2500 g or less fr
registrations.

There were anomalies in using
returns to obtain denominators f
birthweight specific birth prevalen
palsy. Firstly, these data for 1966 we
as the regional records had been
ondly, it was not possible to matc
boundaries covered by the LHS 27/1
and after the 1974 health service
After 1974 the Mersey Regional H
included part of what was previou
County Borough and excluded pa
previously Cheshire County Bo
changes have been allowed for by
subtraction of the appropriate c
health division data on low birthwe
the years 1967–73.

Results

A total of 870 cases of cerebral pa
years 1966–77 inclusive to mothers
Mersey region comprised the registe
that were 'acquired' were excluded
analyses relate to the remaining 685
403 were boys and 282 girls, a male
1·4:1.

Type of cerebral palsy. The distribut
according to type of cerebral palsy is
1. There were 19 cases unclassified b
or loss to follow up before definitive
were recorded.

Completeness of ascertainment. A f
tainment may have been due to d
follow up before the diagnosis was

Table 1 *Distribution of the 685 cases (af*
cases had been excluded) by type of cereb

Type of cerebral palsy	*No (of ca*
Spastic	
Hemiplegic	185
Diplegic	144
Quadriplegic	190
Mixed Hemiplegic	12
Mixed diplegic	5
Mixed quadriplegic	57
Dyskinetic	28
Ataxic	29
Ataxic/dyskinetic	2
Hypotonic	14
Unclassified	19
Total	685

recording of the latter was usually due to migration. From our records it was possible to identify 71 cases whose mothers migrated into the Mersey region after the birth of the affected child. (These cases were not part of the 685 children who were the basis of the analysis in this paper.) In contrast, there were only 38 cases who migrated out of the region after birth. The total population of the region altered little

Table 2 *Annual birthweight specific frequencies and prevalences of cerebral palsy in the Mersey region 1966–77*

Year	*Birthweight group (g)*	*Frequency of cerebral palsy*	*No of live births*	*Prevalence of cerebral palsy per 1000 live births*	*No of neonatal survivors*	*Prevalence of per 1000 survivors*
1966	≤1500	3	Not available	Not available	Not available	Not available
	1501–2500	15	Not available	Not available	Not available	Not available
	>2500	35	Not available	Not available	Not available	Not available
	All birth weights	54	45637	1·18	44485	1·21
1967	≤1500	3	353	8·50	118	25·42
	1501–2500	10	2657	3·76	2491	4·01
	>2500	36	41148	0·87	40373	0·89
	All birth weights	52	44158	1·18	42982	1·21
1968	≤1500	4	375	10·67	151	26·49
	1501–2500	15	2989	5·02	2784	5·39
	>2500	49	40309	1·22	39594	1·24
	All birth weights	69	43673	1·58	42529	1·62
1969	≤1500	8	346	23·12	138	57·97
	1501–2500	9	2966	3·03	2791	3·22
	>2500	46	38940	1·18	38313	1·20
	All birth weights	65	42252	1·54	41242	1·58
1970	≤1500	6	382	15·71	164	36·59
	1501–2500	13	2977	4·37	2818	4·61
	>2500	40	38711	1·03	38000	1·05
	All birth weights	59	42070	1·40	40982	1·44
1971	≤1500	1	297	3·37	127	7·87
	1501–2500	14	2534	5·52	2370	5·91
	>2500	41	38385	1·07	37673	1·09
	All birth weights	57	41216	1·38	40170	1·42
1972	≤1500	1	289	3·46	129	7·75
	1501–2500	15	2459	6·10	2316	6·48
	>2500	56	35088	1·60	34528	1·62
	All birth weights	73	37836	1·93	36973	1·97
1973	≤1500	2	220	9·09	76	26·32
	1501–2500	14	1787	7·83	1699	8·24
	>2500	43	32346	1·33	31777	1·35
	All birth weights	61	34353	1·78	33552	1·82
1974	≤1500	5	254	19·69	98	51·02
	1501–2500	14	1964	7·13	1862	7·52
	>2500	45	30297	1·49	30153	1·49
	All birth weights	64	32515	1·97	32113	1·99
1975	≤1500	2	204	9·80	92	21·74
	1501–2500	15	1639	9·15	1555	9·65
	>2500	31	29403	1·05	29238	1·06
	All birth weights	49	31246	1·57	30885	1·59
1976	≤1500	0	181	0·00	105	0·00
	1501–2500	16	1377	11·62	1325	12·08
	>2500	24	28202	0·85	28042	0·86
	All birth weights	40	29760	1·34	29472	1·36
1977	≤1500	3	193	15·54	95	31·58
	1501–2500	10	1252	7·99	1213	8·24
	>2500	29	26985	1·07	26838	1·08
	All birth weights	42	28430	1·48	28146	1·49
Total	≤1500	38	Not available	Not available	Not available	Not available
	1501–2500	160	Not available	Not available	Not available	Not available
	>2500	475	Not available	Not available	Not available	Not available
	All birth weights	685	453146	1·51	443531	1·54

Significance	≤1500	χ^2 for trend per 1000 live births,	0·22, not significant
		χ^2 for trend per 1000 survivors,	0·96 not significant
	1501–2500	χ^2 for trend per 1000 live births,	15·97, $p<0·001$
		χ^2 for trend per 1000 survivors,	15·08, $p<0·001$
	>2500	χ^2 for trend per 1000 live births,	0·21, not significant
		χ^2 for trend per 1000 survivors,	0·13, not significant

during the study; there was a small increase in population in the early years followed by a compensatory decrease. Therefore, the recorded difference in cases of cerebral palsy between migration in and migration out of the region was presumably an artefact due to incomplete ascertainment of those who migrated out unless there was a differential migration of cases with cerebral palsy relative to the total population. Examination of this discrepancy by year of birth showed that it was evenly spread over the 12 year study period, which means that it is unlikely to have led to a bias in the trends observed.

Trends in the birth prevalence of cerebral palsy. There were 453 146 live births in the Mersey region during the years 1966–77 inclusive, with 685 cases of cerebral palsy, giving an overall birth prevalence of 1·51 per 1000 live births. Annually, the birth prevalence ranged between 1·18 and 1·97 per 1000 live births, but there was no discernible trend over the period studied (χ^2_{1DF} for trend 2·21, not significant).

Table 2 shows annual birthweight specific frequencies and prevalences for cerebral palsy. The 54 cases born in 1966 had to be excluded from the analysis because birthweight specific denominator data for the region were not available, the LHS 27/1 records having been destroyed. An additional 11 cases born in the years 1967–77 inclusive also had to be excluded as their birth weight was not recorded. Trends in birthweight specific prevalences are shown in Figure 1 for two groups, infants with birth weights ≤2500 g and >2500 g There was significant upward trend in prevalence among weight group (χ^2_{1DF} for trend 11 but no trend was observed for inf birth weight (χ^2_{1DF} for trend 0·2 cant). Higher prevalences were c denominator used was the numb

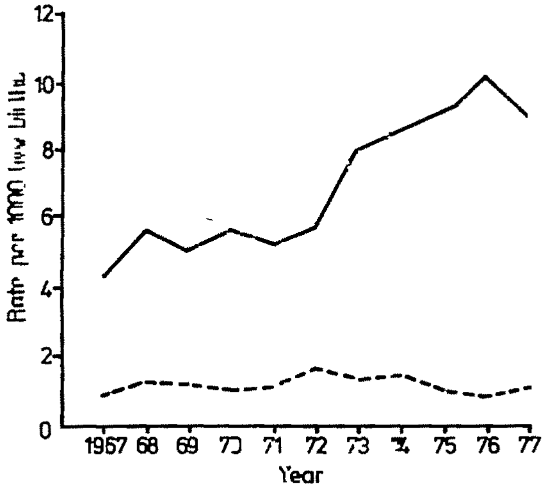

Fig. 1 *Birthweight specific prevalence of cerebral palsy for infants with birth weight ≤2500 g (———) and >2500 g (– – –).*

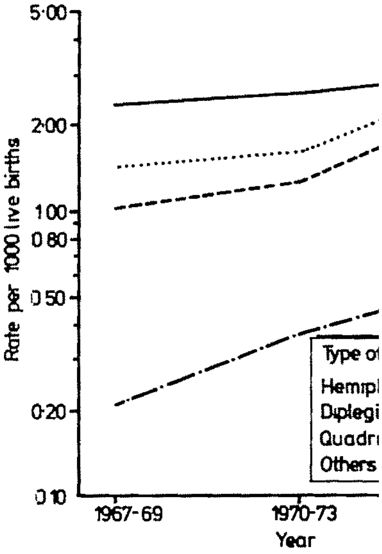

Fig. 2 *Trend by type of cerebral palsy fo (≤2500 g) infants.*

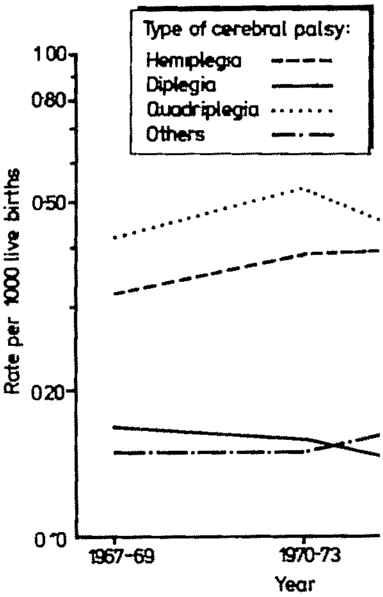

Fig. 3 *Trend by type of cerebral palsy fo birthweight (<2500 g) infants.*

survivors; the trends in prevalences were similar, however, whether live births or survivors were used for the denominator.

Trends in birthweight specific prevalence according to type of cerebral palsy. The data have been grouped for the years 1967–69, 1970–73, and 1974–77. Also the mixed spastic syndromes have been combined with the appropriate spastic type—that is, mixed hemiplegia with spastic hemiplegia, mixed diplegia with diplegia, and mixed quadriplegia with quadriplegia. Among low birthweight infants the upward trend was evident in all types of cerebral palsy (Fig. 2). In none, however, was the trend significant, though this may have been a statistical type II error because the numbers in the samples were small. In contrast, no consistent pattern was obvious in the trend among infants of normal birth weight (Fig. 3).

Thus the overall increase in prevalence among low birthweight infants was the composite result of an increase in prevalence of each type of cerebral palsy.

Discussion

The recrudescence of interest in the epidemiology of cerebral palsy has occurred primarily because of its possible use as an outcome measure for evaluating neonatal special and intensive care. The use of epidemiology in this manner, however, has its problems.

It is tempting to attribute the recent rise of cerebral palsy among low birthweight infants to the development of neonatal special and intensive care and consider them casualties of technological development,[7] but caution must be exercised before coming to this conclusion. If cerebral palsy is an undesired side effect of special care two plausible explanations could be invoked. The immature infant, though born with an intact brain, may, because of its immaturity, be liable to a variety of insults, such as intraventricular haemorrhage and cerebral ischaemia, with its consequent neurological deficit. Implicit in this explanation is that special/intensive care is a cause of cerebral palsy and directly affects the incidence of the syndrome. The alternative explanation is that the neurological deficit is present before birth as a result of genetic or other factors but that improvements in obstetric and neonatal care ensure that these infants now survive so that the prevalence, though not the incidence, of cerebral palsy is affected.

From the epidemiological standpoint it is crucial to distinguish between these alternatives as the prevention of the disability and ultimately an understanding of the aetiology is dependent on knowledge of the incidence. The observation that the increase in prevalence among low birthweight infants occurred with all types of cerebral palsy suggests that the latter explanation is more plausible—that is, that the incidence has not changed but that improved survival rates, particularly among low birthweight infants, have increased prevalence. Furthermore, it is inherently implausible that neonatal intensive care is aetiologically implicated in all forms of the disease.

A third possible explanation of the upward trend in prevalence of cerebral palsy among low birthweight infants relates to an improvement in the completeness of ascertainment. A deficiency in ascertainment is to be expected when the use of health service facilities determines whether an affected child is registered as a case. Such a failure of ascertainment is particularly liable to occur with those children who are least severely affected. The very successes of neonatal intensive care have generated an increasing interest in the routine follow up of low birthweight infants and ensures that the milder cases of cerebral palsy among this group may now be diagnosed and registered, whereas previously they would have been missed, a phenomenon that has been termed 'diagnostic access' bias.[13]

There is a further reason for not attributing the increase in prevalence of cerebral palsy among low birthweight infants to the development of intensive care. Essentially, the period covered by the survey reported here predates the development of intensive care in the Mersey region; a consultant neonatologist was not appointed until 1980. In support of this, if artificial ventilation is used as an index of intensive care, of the 198 infants with cerebral palsy born weighing ≤2500 g during the period 1966–77, only 15 were artificially ventilated. Even if it was assumed that all 15 would not have survived without ventilation, the increase in prevalence of cerebral palsy among low birthweight infants would still have been observed.

If the effectiveness of neonatal intensive care is to be monitored the examination of trends in prevalences of cerebral palsy is not adequate for the purpose, and it is preferable to conduct follow up studies of cohorts of low birthweight infants, ideally among geographically delineated groups, to avoid the bias associated with selectivity of admission to hospital.

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Central nervous system dysfunction and erythrocyte guanosine triphosphate depletion in purine nucleoside phosphorylase deficiency

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SUMMARY Developmental retardation was a prominent clinical feature in six infants from three kindreds deficient in the enzyme purine nucleoside phosphorylase (PNP) and was present before development of T cell immunodeficiency. Guanosine triphosphate (GTP) depletion was noted in the erythrocytes of all surviving homozygotes and was of equivalent magnitude to that found in the Lesch-Nyhan syndrome (complete hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency). The similarity between the neurological complications in both disorders indicates that the two major clinical consequences of complete PNP deficiency have differing aetiologies:

(1) neurological effects resulting from deficiency of the PNP enzyme products, which are the substrates for HGPRT, leading to functional deficiency of this enzyme.

(2) immunodeficiency caused by accumulation of the PNP enzyme substrates, one of which, deoxyguanosine, is toxic to T cells.

These studies show the need to consider PNP deficiency (suggested by the finding of hypouricaemia) in patients with neurological dysfunction, as well as in T cell immunodeficiency. They suggest an important role for GTP in normal central nervous system function.

Deficiency of the enzyme purine nucleoside phosphorylase (PNP:EC 2 4 2.1) was first reported in 1975 in a child with recurrent infection and anaemia.[1] Clinical features in the first nine cases[2–4] have invariably been related to a pronounced reduction in T cell numbers and function, with either normal or enhanced B cell function.[1–7] Deoxyguanosine triphosphate (dGTP) has been found in the erythrocytes and implicated in the T cell dysfunction of the disorder.[2–5] The age at presentation has varied from birth to 6 years Therapeutic approaches to restore immune competence have usually been unsuccessful.[2–5] Most patients have died from viral infection or lymphoma.[1–9] Successful engraftment after haploidentical bone marrow transplantation has been reported recently in a single case.[10]

This paper compares clinical and biochemical findings in our latest case of PNP deficiency with those in two previous kindreds[5 9] and highlights severe developmental retardation as a prominent clinical feature of the disorder. We have also found severe guanosine triphosphate (GTP) depletion in the red cells of all available homozygotes from these kindreds,[5 9 11] in addition to the dGTP accumulation noted earlier by others.[2–4] As the brain has a high requirement for GTP[12] and resembles the human erythrocyte (Fig. 1) in being largely dependent on salvage to maintain GTP concentrations the combined clinical and biochemical findings support a direct relation between the enzyme defect and the neurological dysfunction. They underline the fact that PNP deficiency should be suspected in children with central nervous system (CNS) disorders as well as T cell immunodeficiency and suggest a metabolic basis for this association.

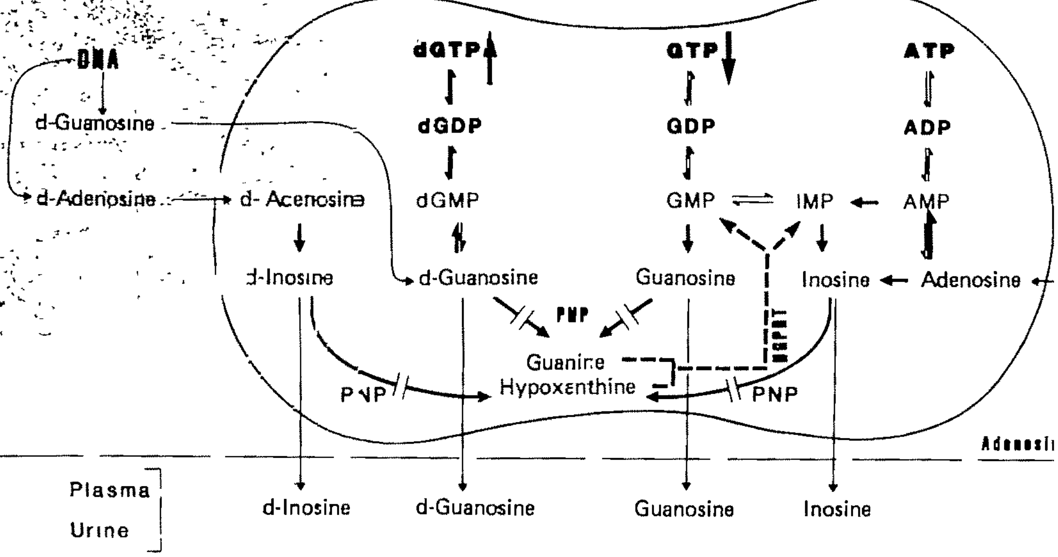

Fig 1 *Pathways of purine metabolism, indicating the importance of PNP for the degradation of deoxyribonucle derived from the turnover of DNA, as well as ribonucleosides arising from ATP and GTP (all shown in bold) durin cell turnover In the absence of PNP (broken arrows) the four PNP substrates indicated accumulate in the plasma a excreted in urine in place of uric acid The potential for dGTP formation after deoxyguanosine accumulation when defective is also shown*

The effect of complete PNP deficiency in restricting substrate availability for HGPRT is evident from the broke showing that HGPRT normally plays a vital role in tandem with PNP for guanine recycling and maintenance o concentrations, particularly when de novo synthesis is absent, as in the human erythrocyte, or limited, as in the brai importance of extracellular adenosine, and hence adenosine kinase, for maintaining ATP concentrations in the red ce to a lack of the normal route of ATP formation from IMP present in nucleated cells, is also indicated

PNP=purine nucleoside phosphorylase, DNA=deoxyribonucleic acid, ATP=adenosine triphosphate, ADP=adenosine diphosphate, AMP= a monophosphate, GTP=guanosine triphosphate, GDP=guanosine diphosphate, GMP=guanosine monophosphate, dGTP=deoxyguanosine triph dGDP=deoxyguanosine diphosphate dGMP=deoxyguanosine monophosphate, HGPRT=hypoxanthine-guanine phosphoribosyltransferase, IMP monophosphate, d-=deoxy

Patients and methods

Case reports.

Family 1

The propositus (case 1) in this family was the first son of healthy Irish parents who were fourth cousins. A full clinical history has been reported.[8] In brief, the infant had considerable developmental delay before an aseptic meningitis at 2 years, from which he made a full recovery At 2 years 8 months he presented with an illness similar to glandular fever. He was unable to walk unsupported and had a crude hand grasp and delayed speech. A spastic tetraparesis was clinically evident. He died of malignant lymphoma of the immunoblastic type shortly after PNP deficiency was defined.

A second boy (case 2) was born in June 1980 and PNP deficiency was confirmed at birth. He was kept under close clinical observation while different treatments were given in an attempt to ameliorate the progressive immunodeficiency [5] Excessive lag and irritability were noticeable by 3 m Extensive neurological investigation reveale organic lesion or viral infection The infant after remained profoundly hypotonic with dev mental delay in all spheres. Hypertonicity lower limbs developed before his death at 2 from an acute para-influenza type 111 infectio pneumonia. There was no structural brain les postmortem examination.

Family 2

The propositus (case 3) was an Arab girl, the child of parents who were first cousins. Full are given elsewhere.[9] She presented with anae seven days' duration at 4 years in January 19 spastic tetraparesis was noted Developmental was first investigated at 1 year General ph examination showed hypertonia and exagge tendon reflexes, involving all limbs An int tremor was also present. There was severe developmental retardation, with motor involvement (equal to a child of 1 year) being more severe than intellectual development (equivalent to a child of 2·5 years). The child had started to sit at 1 year and stand at 3 years and walked unsteadily on tiptoe with help at 3 years 9 months. Investigations showed a child with anaemia with a positive result of a direct Coombs test and severe T cell immunodeficiency [9] A computed tomogram of the brain and electroencephalogram yielded normal results. The child subsequently succumbed to viral infection at the age of 4 years 6 months. Permission for postmortem examination was refused.

Family history revealed an elder sister (case 4) who had died at 4 years of chickenpox complicated by pneumonia and carditis and had also been severely developmentally retarded and suffered repeated chest and ear infections. (She was considered a homozygote for PNP deficiency from the similarity in the case history). An 11 month old brother (case 5) showed similar abnormalities to the propositus CNS involvement was evident from poor head control, generalised hypotonia with inability to stand, and a delay in fine motor milestones. Only limited investigations were permitted, but retardation remains the principal problem. Despite the severe T cell immunodeficiency,[9] there have been no episodes of infection over the past 12 months.

Family 3

The propositus in this new kindred (case 6) was the fourth child of healthy, unrelated parents One child had died at birth The two surviving siblings are healthy. He was noted to have mild left hemiparesis and delayed motor development aged 14 months and at the time of study was attending a special school. He presented in March 1986 at the age of 4 years 5 months with Coombs positive autoimmune haemolytic anaemia (haemoglobin 8·9 g/dl) and thrombocytopenia (18×10^9/l) after the latest of a series of pulmonary infections. He was shown to have severe T cell deficiency with lymphopenia and lack of mitogen and alloantigen responses; immunoglobulin concentrations were normal (IgG 8·9, IgA 0·51, and IgM 1·1 g/l) At this time he was making reasonable developmental progress, with the non-progressive hemiparetic cerebral palsy as his only neurodevelopmental problem. He died at 4 years 6 months of complications related to immunosuppression of graft versus host disease contracted from a platelet transfusion. Permission for postmortem examination was refused.

Biochemical methods. Purine nucleoside concentrations in plasma and urine and nucleotides in red cells were determined using a Waters (Millipore-Waters, Harrow, Middlesex, England) trimodule fully automated high pressure liquid chromatography system coupled to a 5μ APS-Hypersil column, or a 5μ Spherisorb ODS1 column (25 cm × 4·9 mm, Hichrom, United Kingdom), for the separation of nucleotides, or nucleosides and bases, respectively.[11 13–15] The method used for determination of PNP activities, as well as the activity of the other purine enzymes—namely, adenosine deaminase, adenine phosphoribosyltransferase, and hypoxanthine–guanine phosphoribosyltransferase (HGPRT)—in lysed red cells using high pressure liquid chromatography, has also been reported.[14] Studies with 8–[14C] labelled deoxyguanosine, using intact red cells, were also carried out to exclude the possibility of a labile enzyme detectable only in intact cells (not lysed cells). They were processed using a radiodetector (Reeve Analytical, Glasgow, Scotland) coupled to the above high pressure liquid chromatography system as previously described.[15] S-adenosylhomocysteine hydrolase activity was determined by the method of Kaminska and Fox [16]

Results

Purine enzymes. The propositus in family 3 (case 6) was found to lack any detectable PNP activity in lysed erythrocytes, as previously found for cases 2, 3, and 5 (Table 1). Completeness of the enzyme defect and exclusion of the presence of a labile enzyme was confirmed by incubation of intact red cells from case 6 with 8–[14C] deoxyguanosine. (This showed no metabolism of substrate to guanine, although detectable amounts of deoxyguanosine triphosphate were formed. Results not shown.) Both parents and one sibling in family 3 showed heterozygote PNP activities in lysed red cells (Table 1) The results are in accordance with the recessive mode of inheritance reported in the disorder.[2–4 8]

The presence of normal HGPRT activity in case 6 (Table 1), as in cases 2, 3, and 5, was also confirmed by studies in intact red cells (results not shown). Of the other purine enzymes, both adenine phosphoribosyltransferase and adenosine deaminase were again raised in case 6 (Table 1), a finding noted in some but not all homozygotes [1–7 9] Low S-adenosylhomocysteine hydrolase activities (patient range 1·7–3·0 nmol/mg Hb/h. control range 3·6–9·0 nmol/mg Hb/h) were also found, as reported earlier by others in this disorder.[2–4 9 16] Extremely low activities of this enzyme were first noted in adenosine deaminase deficiency, the companion purine disorder presenting as severe combined

Table 1. *Specific activities of four different purine enzymes in the parents and the surviving siblings in family 3, compa with previous results in cases 2, 3, and 5.[5 9] Plasma and urine purine concentrations in the four homozygotes show accumulation of the four nucleosides inosine, guanosine, deoxyinosine, and deoxyguanosine in place of uric ac*

	Purine enzyme activity in lysed erythrocytes (nmol/mg Hb/h)			
	PNP	*ADA*	*APRT*	*HGPRT*
Family 3				
Case 6	<0 1	108	70	194
Sister	4668	65	25	152
Brother	1940	99	25	139
Father	1988	65	19	134
Mother	2367	93	33	154
Family 1				
Case 2	<0 1	62	45	111
Family 2				
Case 3	<0 1	185	67	138
Case 5	<0 1	117	42	160
Control (n=200)				
Mean	4500	70	24	105
(SD	(722)	(12)	(4 8)	(16 5)

Case No	*Purine concentrations in body fluds* *Plasma (μmol/l)*					*Urine (mmol/mmol)*				
	Uric acid	*Inosine*	*Guanosine*	*Deoxyinosine*	*Deoxyguanosine*	*Uric acid*	*Inosine*	*Guanosine*	*Deoxyinosine*	*Deoxyguano*
6	T	62	23	19	14	T	1 10	0 36	0 36	0 29
2	7	46	9	2	2	T	1 68	0 57	0 32	0 29
3	T	41	11	7	6	T	1 90	0 87	0 38	0 41
5	5	49	13	6	5	T	1 44	0 74	0 41	0 33
Control range	(130–230)	—	—	—	—	(0 2–1 0)	—	—	—	—

PNP=Purine nucleoside phosphorylase: ADA=adenosine deaminase, APRT=adenine phosphoribosyltransferase, HGPRT=hypoxanthine-gu phosphoribosyltransferase.
T=Trace
—=Not normally detectable

Table 2 *Mean red cell nucleotide concentrations in the four homozygotes from the three PNP deficient kindreds compa with the mean values from 20 control children and seven patients with HGPRT deficiency, showing the correlation betw GTP concentrations and the degree of neurological involvement as well as the accumulation of dGTP in PNP deficient cells (gout/retarded=dysarthric, spastic gait, but no self mutilation)*

Case No	*Red cell nucleotides (μmol/l packed cells)*								
	ATP	*ADP*	*AMP*	*GTP*	*GDP*	*dGTP*	*dGTP*	*NAD*	*UD*
Cases with PNP deficiency									
6	1284	134	13	9	7	7	4	319	126
2	1044	130	10	5	5	3	3	276	149
3	1011	132	39	6	4	5	4	307	37
5	1564	145	12	5	4	4	5	213	110
Cases with HGPRT deficiency									
1*	1543	130	8	9	6	—	—	193	116
2*	1813	245	13	12	10	—	—	226	139
3†	1273	104	8	14	8	—	—	162	87
4†	1273	91	15	16	8	—	—	221	123
5‡	1207	170	21	51	15	—	—	140	73
6‡	1125	205	4	43	12	—	—	239	64
7‡	1193	195	6	45	18	—	—	151	105
Controls (n=20)									
Mean	1140	144	13	68	15	—	—	72	44
(SD)	(72)	(47)	(8)	(11)	(3)	—	—	(15)	(8)

PNP=Purine nucleoside phosphorylase, ATP=adenosine triphosphate, ADP=adenosine diphosphate, AMP=adenosine monophosphate, GTP=guan triphosphate, GDP=guanosine diphosphate, dGTP=deoxyguanosine triphosphate, dGDP=deoxyguanosine diphosphate, NAD=nicotinamide ad dinucleotide, UDPG=uridinediphosphate glucose, HGPRT=hypoxanthine-guanine phosphoribosyltransferase, —=not normally detectable
*Lesch-Nyhan syndrome
†Gout/retarded=dysarthria, spastic gait but no self mutilation
‡Gout/no neurological complications

immunodeficiency,[16-18] but the association, if any, with the immunodeficiency remains undefined.

Plasma and urine purine concentrations. Table 1 also shows that case 6 likewise accumulated high concentrations of the four PNP substrates, inosine, guanosine, deoxyinosine, and deoxyguanosine, in place of uric acid The latter was virtually undetectable in both plasma and urine, confirming the completeness of the enzyme defect in all the homozygotes we studied. Excretion measured as an index of creatinine showed the purine overproduction characteristic of this disorder (three- to fourfold normal). Renal clearances relative to the glomerular filtration rate for the four nucleosides indicated net tubular secretion

Erythrocyte nucleotide concentrations. Mean red cell nucleotide concentrations in case 6 (Table 2, Fig. 2) showed very low guanosine triphosphate/guanosine diphosphate concentrations, as noted earlier in cases 2, 3, and 5,[5 9] associated with raised deoxyguanosine triphosphate/deoxyguanosine diphosphate, nicotinamide adenine dinucleotide, and uridinediphosphate glucose concentrations.

Mean red cell nucleotide concentrations from patients with HGPRT deficiency are also shown in Table 2 for comparison and show that red cell GTP

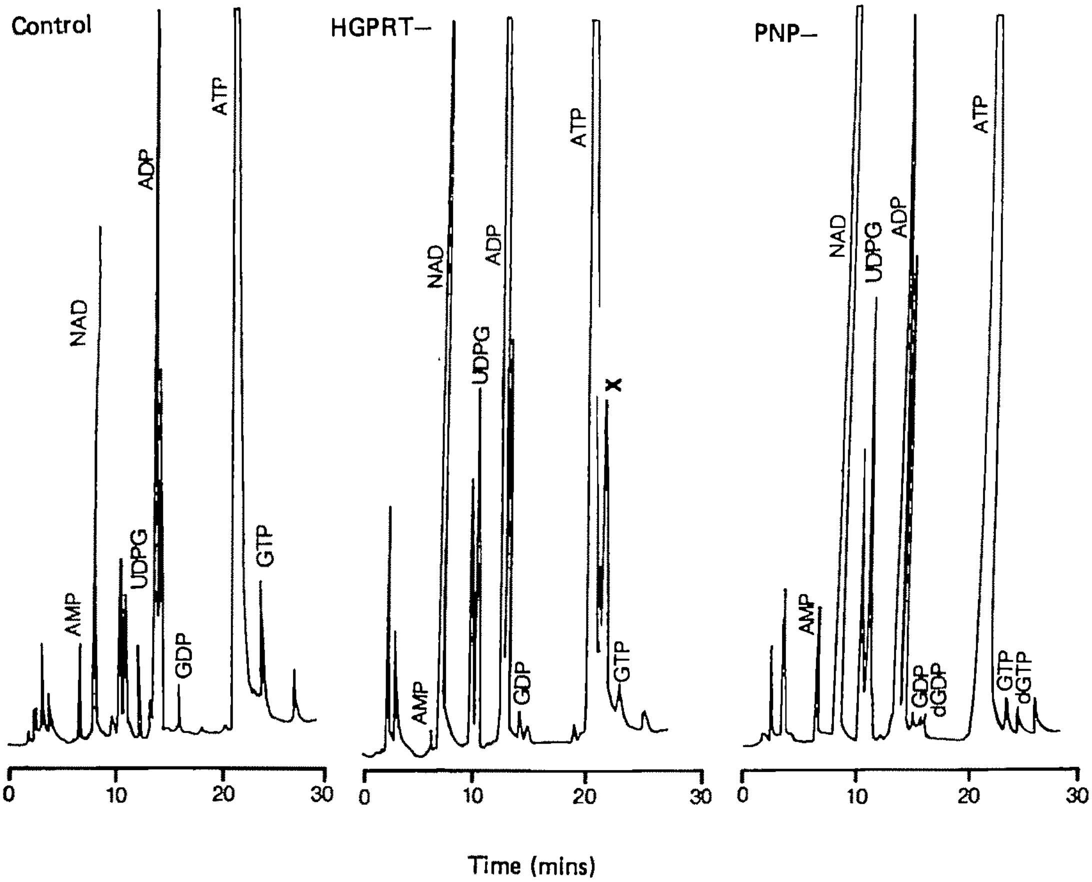

Fig 2 *High performance liquid chromatography traces at 254 nm and 0 05 aufs after injection of 25 µl of extract from the red cells of case 6 (PNP–) and a case with the Lesch-Nyhan syndrome (HGPRT–), showing the severe GTP and GDP depletion compared with the control and the presence of two additional peaks corresponding to dGDP and dGTP in the PNP deficient cells (Peak marked X in the HGPRT– cells is ZTP 5-amino-4-imidazolecarboxamide ribotide.)*

PNP=Purine nucleoside phosphorylase, HGPRT=hypoxanthine-guanine phosphoribosyltransferase, ATP=adenosine triphosphate, ADP=adenosine diphosphate, AMP=adenosine monophosphate, GTP=guanosine triphosphate, GDP=guanosine diphosphate, dGTP=deoxyguanosine triphosphate, dGDP=deoxyguanosine diphosphate, NAD=nicotinamide adenine dinucleotide, UDPG=uridinediphosphate glucose

depletion was likewise[9] a characteristic of severe HGPRT deficiency (Lesch-Nyhan syndrome) and tended to reflect the severity of the CNS involvement. Red cell GTP depletion was not found in the four patients with partial HGPRT deficiency in whom CNS function was normal.

Discussion

The purpose of this report was to highlight the neurological abnormalities that were a prominent clinical feature in six patients from three PNP deficient families. It should be emphasised, therefore, that immunodeficiency may not be the presenting symptom in this disorder. Neurological involvement was also present in four of the first nine published cases, but it was questioned whether this was secondary to viral infection, possibly contracted by immunisation with live virus.[2] Our observations indicate that CNS viral infection is an unlikely cause of the neurological deficit seen in these patients. Case 2 was investigated from birth and showed head lag and excessive irritability at 3 months.[5] Our latest case had neurological problems that required attendance at a special school, well before the onset of autoimmune disease. Spastic tetraparesis was present in three siblings from the first Dutch kindred,[2 3] a recent Dutch case was investigated initially for spastic diplegia and behavioural disorders, not immunodeficiency.[6] Furthermore, neurological complications have not been present in any of the 12 children with adenosine deaminase deficiency and severe combined immunodeficiency that we have studied.[18]

Neurological symptoms have now been described in 50% of cases with PNP deficiency. Of the remainder, there has been no mention of CNS function in five homozygotes,[2 6] while mild neurological problems associated with an intention tremor were noted in one case, with a total absence of neurological problems in three others.[2] The four latter cases, however, had some residual PNP activity. Two further cases exist that have not been reported in detail and apparently do not have neurological involvement, but again these are in the older age group suggesting some residual enzyme. (Hershfield MS Personal communication.) Thus the range of neurological involvement apparently equates well with the severity of the enzyme deficiency. The other noteworthy finding in this report is that severe erythrocyte GTP depletion seems to be characteristic of PNP deficient kindreds with neurological involvement (Zegers BJM. Personal communication.) GTP depletion has also been a consistent finding in patients with the Lesch-Nyhan syndrome (severe HGPRT deficiency),[19] but it has not been found in partial HGPRT deficiency without neurological involvement (sex linked recessive gout/urolithiasis).

These findings suggest an important link between GTP concentrations and normal CNS function GTP is known to be essential both for sustained macromolecular synthesis and neurotransmission within the CNS. Consequently, restriction of substrate supply to HGPRT, due to defective PNP activity (Fig 1), could be as damaging to either of these functions as a defect in HGPRT itself This hypothesis is supported by the fact that the clinical progress of case 2 bore many similarities to that described for children with the Lesch-Nyhan syndrome, where generalised muscular hypotonia from infancy is considered to be the basic abnormality on which torsion dystonia is subsequently superimposed[12] HGPRT activity is higher in the CNS than in any other tissue, and in the neonatal period the ratio of HGPRT salvage activity to de novo synthesis increases considerably after the main burst of neuroblast and neuroglial proliferation.[12] The absence of any anatomical or histopathological lesions in the brain in the Lesch-Nyhan syndrome suggests that the enzyme deficiency produces neurological dysfunction by interfering with brain function rather than brain morphogenesis.[12] Extensive neurological investigation in case 2 also revealed no anatomical lesion.[5] This was confirmed at postmortem examination.

The combined clinical and biochemical results suggest that CNS dysfunction in PNP deficiency is a direct consequence of the enzyme defect and relates to an inherent inability to sustain GTP at concentrations essential for normal function, with the red cell, as in HGPRT deficiency, reflecting a wider deficit in tissues, such as brain, that also depend on salvage for maintaining GTP concentrations. Whether the finding of GTP depletion and/or the associated accumulation of deoxyguanosine triphosphate in platelets as well as red cells[9] is also important for the immune response is unknown. With the exception of case 6, platelet numbers have been normal, but GTP depletion in vitro has been linked with defective synthesis of deoxyribonucleic acid in lymphoid cells.[20] As immunodeficiency is not a facet of the Lesch-Nyhan syndrome, however, it would seem that GTP depletion per se is not implicated in the gradual attrition of T cell function in PNP deficiency.

In summary, this study underlines the fact that immunodeficiency may not necessarily be the presenting abnormality, or of the greatest immediate concern to the family, in patients with PNP deficiency. The enzyme defect should be considered in children with developmental delay and neurological dysfunction. Autoimmune haemolytic anaemia is also a recognised mode of presentation.[2 9] The diagnosis is suggested by the finding of hypouricaemia. Measurement of PNP activity and purine concentrations in body fluids will be essential to confirm the metabolic basis for the defect,[21] while red cell GTP concentrations may be a useful guide to the degree of CNS involvement. The studies also indicate that there may be potential hazards associated with the development of PNP inhibitors as immunosuppressants for different malignant states.

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Comparison in use of health services between a deprived and an endowed community

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SUMMARY Two hundred and twenty eight deprived children were compared with a matched sample of more endowed children living in the same urban area. Both groups were served by the same experienced primary health care team. The deprived group had a significantly higher number of general practitioner consultations and admissions to hospital (aged under 5) and a significantly higher recorded prevalence of mental and psychological disturbance (aged 5–15). Accident and emergency attendances were significantly higher for the deprived group throughout childhood, as were non-attendances for medical care appointments. The deprived group had much worse rates of immunisation and significantly later immunisations; practical measures subsequently adopted to improve this uptake of immunisation are described.

Low social class has long been associated with comparatively poor health and low uptake of preventive care. The Black report attributed this to a self perpetuating cycle of socioeconomic deprivation, and the first objective of the report's recommendations was to give deprived children a better start in life.[1]

Our practice has consistently tried, in an unstructured way, to provide equal health care to patients of different social backgrounds. To assess our success, we have compared the recorded morbidity and state of immunisation of 228 matched pairs of deprived and more endowed patients under 16 years of age. The deprived group lived in the Blue Hall council estate, Stockton-on-Tees, a locality of severe socioeconomic deprivation. The more endowed controls, matched for sex and age, lived in a defined neighbouring area of pleasant private housing estates in north Norton, equidistant (one mile) from our practice premises. This work was part of a survey of patients of all ages from these two communities.[2]

Our practice contains five full time and one part time experienced general practitioners, frequent trainees and ancillary staff to the reimbursable maximum of two per doctor. It has three attached district nurses, usually two but sometimes three health visitors, and effective working liaison with a social worker, community psychiatric nurse, and marriage counsellor in short, a comprehensive if slightly shoestring primary health care team to serve 15 700 urban patients. It has excellent A4 medical records,[3] supplemented by a microcomputer, a personal list policy, and no private patients and performs its own out of hours calls. Because of the close proximity of a large hospital, the practice is rarely involved in the initial treatment of accident and emergency cases

Method

The sampling frame was the age-sex register of the practice on 30 September 1984. The deprived group comprised all 228 patients from the Blue Hall council estate aged under 16 who had been registered with the practice for at least a year or born into the practice during that year. They comprised roughly 30% of the children on the estate. Each deprived patient was matched by sex and nearest birthdate with a control patient who satisfied the same conditions and lived in the defined endowed area. Close matching of birthdates was achieved.

All data were abstracted from each patient's comprehensive A4 medical record folder, ignoring entries after 30 September 1984. The number of entries on the included sheet 'summary of important illnesses and investigations' was noted, these having previously been entered by our trained staff using rigid guidelines.[3] These entries were divided into physical and mental/psychological conditions. The numbers of consultant referrals and admissions to hospital were obtained from an analysis of the date ordered correspondence with hospital departments. Attendances at hospital accident and emergency departments were obtained from the 'casualty slips' returned by the hospital and invariably filed in the folders. Non-attendances at prearranged health care appointments of all types were abstracted for the last five years (since birth for children under 5). Because of the greater frequency of general practitioner consultations their numbers were abstracted for only three years, excluding telephone, nurse, and health visitor consultations.

The details and dates of immunisations were noted. 'Possible' and 'actual' scores were given: 4 for each triple immunisation plus polio (1 for each element), 4 for measles, and 3 for the diphtheria, tetanus, and polio booster A child scored for receiving an immunisation at any age, excluding school leaving immunisations. In the absence of an immunisation it was necessary to postulate an age by which the child could reasonably be considered to have 'defaulted' on that immunisation· the 'deadline' ages used for this purpose were 6, 9, and 12 months for first, second, and third triple/polio and 2 and 5 years for measles and booster, respectively. Infection or contraindication before the deadline age reduced the possible score. Two examples may clarify this: a child of 10 months who had received only the first diphtheria, tetanus, and polio with pertussis immunisation medically contraindicated would have an actual score of 3 and a possible score of 6, a child aged 6 who had received only the first and second triple/polio immunisations and had contracted measles at 21 months (before the deadline age) would have an actual score of 8 and a possible score of 15. Actual score as a percentage of possible was calculated for each child.

For this matched pair survey the statistical tests used were the Wilcoxon test for quantitative data and the McNemar test for categorical data. In one stated case where matched pairs were not being compared the χ^2 test was used. All statistical significances were based on two tailed tests.

Results

Morbidity. (Table 1). There were no significant differences between the deprived children and

Table 2 *Total occurrences of mental/psychological afflictions in deprived and control children grouped according to age*

	Age group (years)			
	Under 5 (81 pairs)		*5–15 (147 pairs)*	
	Deprived	*Control*	*Deprived*	*Control*
Non-accidental injury	1		9	
Social/emotional problem	2		7	
Behavioural problem	1		7	1
Educationally/mentally subnormal			4	1
Speech/language problem	1		1	2
Hyperkinetic syndrome			1	1
Gilles de la Tourette's syndrome				1
Total	5	0	29	6

Table 1 *Comparison of recorded morbidity in deprived and control children grouped according to age*

	Children group	*Age group (years)*					
		Under 5 (81 pairs)			*5–15 (147 pairs)*		
		No (%) of patients	*Total occurrences*	*Significance*	*No (%) of patients*	*Total occurrences*	*Significance*
Serious illnesses							
Physical	Deprived	22 (27)	29		78 (53)	137	
	Control	27 (33)	29		72 (49)	122	
Mental	Deprived	5 (6)	5		25 (17)	29	
	Control	0 (0)	0		4 (3)	6	***
Consultant referrals	Deprived	19 (23)	22		44 (30)	61	
	Control	15 (19)	20		45 (31)	74	
Hospital admissions	Deprived	27 (33)	49		41 (28)	59	
	Control	12 (15)	15	**	34 (23)	55	
Casualty attendances	Deprived	36 (44)	67		87 (59)	232	
	Control	23 (28)	29	**	72 (49)	117	***
General practitioner consultations	Deprived	77 (95)	713		118 (80)	577	
	Control	70 (86)	477	**	130 (88)	721	*(Controls worse)

*At 5% level 0 01<p<0-05
**At 1% level 0 001<p<0 01
***At 0 1% level p<0 001
All data abstracted over five years, except general practitioner consultations (three years)

controls as far as recorded serious physical illnesses and consultant referrals were concerned.

Mental or psychological afflictions were much more prevalent among deprived children than controls, particularly in the 5–15 age group where the ratio was almost 3 to 1. The most common items were non-accidental injuries, social/emotional problems associated with parental inadequacies, and behavioural problems (Table 2).

Admissions to hospital were three times as high for the deprived children aged under 5 as for their controls, but there was no significant difference in the 5–15 age group. Casualty attendances by deprived children were about twice as high as controls in both age groups. Compared with the controls, general practitioner consultations for the deprived group were 50% higher for those under 5 but 20% lower for those 5–15.

Table 3 *Comparison of immunisation state in deprived and control children grouped according to age. Values are No (%)*

	Age group (years)			
	Under 5 (69 pairs)		*5–15 (85 pairs)*	
	Deprived	*Control*	*Deprived*	*Control*
No immunisation	10 (14)	0 (0)	11 (13)	0 (0)
Part immunisation (%):				
1–24*	2 (3)	0 (0)	11 (13)	1 (1)
25–49	8 (12)	1 (1)	19 (22)	5 (6)
50–74	10 (14)	3 (4)	17 (20)	13 (15)
75–99	9 (13)	7 (10)	14 (16)	35 (41)
Full immunisation for age	30 (43)	58 (84)	13 (15)	31 (36)
p Value (at 1% level)	<0·001		<0·001	

*Children under 6 months old were omitted.

Non-attendances. For prearranged health care appointments (therapeutic and preventive combined), 20 deprived and three control children under 5 had one or more non-attendances; for the 5–15 age group the corresponding figures were 36 deprived and 12 control children (p<0·001 for both age groups).

Immunisations. Immunisation data for the 81 pairs aged under 5 seemed reliable, but the data for 62 of the 147 pairs aged 5–15 were marred by uncertainty or complete absence for one or both members who had arrived from other practices. Comparison of immunisations for this age group was therefore restricted to the remaining 85 pairs.

Deprived children had much worse immunisation scores than their controls in both age groups (Table 3). About 86% of deprived babies were presented for the first triple immunisation, but the proportion declined to about 60% by the third triple immunisation and less than 50% for the booster (Table 4). Five deprived children (but no controls) in each age group were restarted on a new course of triple immunisations after a lapse, but in only two of these 10 cases was the renewed course completed. Three deprived parents (but no controls) refused all immunisations for their children. Four other deprived parents (and two controls) refused measles immunisation. More deprived parents refused pertussis immunisation than control parents, although fewer parents in both groups did so in the last five years (Table 4).

Measles was the only immunisation for which previous infection and contraindication (at that time eczema) proved important. The breakdown (Table 5) again showed the poorer state of the deprived children. For both deprived and control children,

Table 4 *Immunisations given to (or medically contraindicated in) deprived and control children grouped according to age. Values are No (%)*

	Age group (years)						
	Under 5				*5–15 (85 pairs)*		
	(Pairs)‡	*Deprived*	*Control*	*Significance*	*Deprived*	*Control*	*Significance*
First triple/polio	(69)	59 (86)	69 (100)	**	73 (86)	84 (99)	**
Second triple/polio	(67)	52 (78)	66 (99)	***	62 (73)	83 (98)	***
Third triple/polio	(62)	39 (63)	60 (97)	***	51 (60)	79 (93)	***
Measles	(51)	34 (67)	44 (86)	*	31 (36)	57 (67)	*
Booster	(15)	7 (47)	13 (87)		36 (42)	77 (91)	***
Pertussis omitted (without contraindication)		20 (29)	6 (9)	**	45 (53)	33 (39)	(†)

*At 5% level 0·01<p<0·05
**At 1% level 0·001<p<0·01
***At 0·1% level p<0·001
(†)At 10% level 0·05<p<0·1
‡For those under 5 fewer pairs were eligible for each successive immunisation

Table 5 *Measles immunisations in deprived and control children grouped according to age Values are No (%)*

	Age group (years)			
	Under 5 (51 pairs)		5–15 (85 pairs)	
	Deprived	Control	Deprived	Control
Immunisation given	20 (39)	35 (69)	19 (22)	41 (48)
Medically contraindicated	5 (10)	7 (14)	6 (7)	10 (12)
Infection before 2 years	9 (18)	2 (4)	6 (7)	6 (7)
Defaulted or refused	17 (33)	7 (14)	54 (64)	28 (33)
p Value*	0 001<p<0 01†		<0 001‡	

*χ^2 test
†At 1% level
‡At 0 1% level

however, those under 5 showed a distinct improvement compared with those 5–15

The 1984 national rates of immunisation[4] for diphtheria, tetanus, and polio were 84%,[4] which compared with 61% for our deprived children aged under 5 and 97% for their controls. Corresponding figures nationally, for our deprived children, and for our controls for pertussis were 52%, 44%, and 87% and for measles were 56%, 39%, and 69%, respectively

Median immunisation dates from birth were significantly later for deprived children. For those aged 5–15 this time lag in median dates varied from seven to 22 weeks for various immunisations For those under 5, however, compared with those 5–15, not only did the median dates of the controls improve (except for measles) but also the time lag for the deprived children of two to four weeks for the various immunisations was considerably smaller.

Discussion

Our survey data together with 1981 census statistics[4] give the following broad picture of the typical Blue Hall estate deprived child. There is roughly a 60% chance that his father is unemployed and over a 50% chance that the family is of social class IV or V. Likewise, there is a 50% chance of his having three or more siblings or alternatively a 10% chance that he belongs to a single parent family. There is over a 40% chance that his mother suffers from or has had at least one mental or psychological ailment and a probability that she is worse than her more endowed control on all other morbidity criteria. There is a 90% chance that one parent smokes and almost a 50% chance that both do. The family lives in crowded deprivation amid poor surroundings, has a poor diet, consumes a fair amount of alcohol, and almost certainly has no telephone or car. Within that setting it is not surprising that the children reflect the high morbidity, high rate of non-attendance, and low uptake of preventive care of their elders in this deprived community.

Deprived children under 5 had a significantly higher number of admissions to hospital and general practitioner consultations than their controls (their consultant referrals are understated because consultant attention in hospital was not included) These differences may be attributed partly to the generally poorer health of heavier smoking deprived mothers during pregnancy and thereafter and partly to the deprived smaller infant's adverse environment, which may include cold, poor diet, over crowding (inducing cross infection), lack of hygiene, and parental inadequacy or neglect. Sick, small babies in poor social circumstances are returned to hospital more promptly by general practitioners even for fairly minor degrees of illness.

It is interesting that, in contrast with those under 5, deprived children aged 5–15 had 20% fewer general practitioner consultations than their controls and that their number of admissions to hospital was not significantly higher. One possible reason is that recurrent illness in infancy may confer a measure of immunity and hardiness later in childhood. A more likely explanation is that deprived children do not receive medical attention as often as they might, evidenced by their much higher non-attendances for medical appointments; thus some morbidity goes unrecorded. The higher morbidity associated with deprivation returns later in life.[2]

Mental disturbance among deprived children is hardly surprising, for parents unhappy amid the pressures of crowded deprivation will spin off behavioural problems onto their children. Contributory factors may be family 'rows' and instability, excessive noise and stress, poor recreational facilities, and inability to get away on holiday. Non-accidental injuries tend to be commoner in lower social classes.[5] A Newcastle study found that lower social class among children was associated with lower intelligence quotient, more borderline and educational subnormality, and more behavioural problems.[6]

The poor environment of deprived children undoubtedly contributes to their high casualty rate. Perusal of hospital casualty slips suggests that many of their home accidents result from hazards unforeseen or unheeded by parents, together with difficulty in supervising large families, while lack of suitable space to play inside and outside the home results in hazardous street activities.

Rates of immunisation showed the biggest disparity between deprived and endowed children. We attribute the poor state of the deprived group almost entirely to default rather than to ailments when immunisations were due. This results partly from the apathy of parents in the deprived group and partly from distrust: the anti-immunisation lobby with its banner headlines has had greatest impact on uninformed parents of low education and intelligence. The effect of the anti-pertussis campaign is evident in both groups of older children but is clearly diminishing in those under 5. More deprived children and controls are receiving immunisations and at earlier median ages, and the deprived children seem to be catching up somewhat on the controls, although they are still well behind

Morbidity associated with deprivation will continue while that deprivation exists. The general practitioner can do little except attempt to cure the morbidity, help his deprived patients by counselling (particularly with regard to contraception and family limitation), and try to ensure that they receive the maximum of preventive care. For children that means immunisation and for their mothers preconception counselling and intensive antenatal care.[8] As the deprived children under 5 visit the doctor more often than their controls opportunities for immunisation manifestly exist, clearly, we have not been making the most of them. To improve uptake of immunisation we have adopted the following measures for an open ended trial:

(1) For each deprived patient, whether child or adult, the front of the A4 medical record now shows the outstanding immunisations for all children in that household Thus immunisation can be discussed and proffered for every child no matter who consults
(2) When a child presents for any reason the doctor will, if appropriate, offer any outstanding immunisation. This is implemented immediately if possible as the structured system of making return appointments is largely ineffective.
(3) We have written to each household listing the outstanding immunisations of each child. Progress is monitored and reminders sent regularly to those who do not respond.
(4) Our health visitors have household lists of outstanding immunisations, which they discuss and encourage when visiting.

Our deprived community, although uncomplicated by sizable ethnic or religious minorities, is probably typical of many in Britain in the 1980s. Unfortunately, these deprived people are not obtaining the full benefits of the free at the time health care ordained by the welfare state to help counter social inequality

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Ipratropium bromide and airways function in wheezy infants

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SUMMARY The airway response to nebulised ipratropium bromide was studied in 17 chronically or recurrently wheezy infants aged 4–15 months. The peripheral airway response was assessed by the change in maximum flow at functional residual capacity ($\dot{V}$max FRC) and the upper and central airway response by the change in specific airways resistance. The significant reduction in specific airways resistance after treatment with ipratropium bromide signified an improvement in central and upper airway function. No change was found, however, in $\dot{V}$max FRC and hence in peripheral airway function. It seems that, as in older subjects, inhaled antimuscarinic, anticholinergic drugs have their maximum effect on the large airways, and this may explain their lack of effect in the management of acute bronchiolitis.

Evidence for the effectiveness of antimuscarinic, anticholinergic agents, such as ipratropium bromide, in the management of wheezy infants remains controversial. Given as a single dose, ipratropium bromide has been shown to diminish the airways resistance, as measured in the lung function laboratory,[1] but has not been shown to confer any important clinical benefit during a small clinical trial.[2]

An explanation for this discrepancy is to be found in the physiological methods that have been used to assess the airway response and the probable site of maximum effect of anticholinergic agents in the airway. In the past, techniques for measuring airways resistance during quiet breathing in infancy have been predominantly influenced by changes in the upper airways (nasopharynx and glottis) and the large central airways. Measurements of airways resistance are fairly insensitive to changes in peripheral airways function. The maximum site of action of inhaled anticholinergic agents is on central airways,[3] coinciding with the site of maximum density of muscarinic receptors.[4] Thus, although improvement in the value of airways resistance might be expected to infer clinical benefit, without an improvement in peripheral airway function such benefit might not occur.

To test this hypothesis we studied 17 infants and obtained measurements of airways resistance, an index of upper and central airways function, and measurements of maximum expiratory flow at functional residual capacity ($\dot{V}$max FRC), an index of peripheral airways function.[5 6] Measurements were made before and after the administration of nebulised ipratropium bromide, a poorly absorbed antimuscarinic, anticholinergic agent, in a group of wheezy infants.

Patients and methods

Patients. Seventeen infants (mean age 7·3 months, range 4–15 months) with a history of wheezing of between one and seven months were studied Twelve infants had persistent wheezing and five recurrent episodes of wheezing, with an interval phase varying from one day to five months between acute attacks. Thirteen of the infants were wheezy on the study day.

Eight of the infants had a first degree family history of asthma or eczema. The parents of eight infants were smokers. Five infants had previously been treated with ipratropium bromide, and two had been reported to show clinical benefit. No infant had received treatment with bronchodilator within 24 hours of testing Before the study, each child was sedated with chloral hydrate 100 mg/kg body weight.

The approval of the local ethics committee and informed parental consent were obtained for all studies, which were carried out as part of the clinical assessment of the children.

Methods.

Lung function tests

After the infants had fallen asleep they were placed in a whole body plethysmograph, and baseline measurements of thoracic gas volume and initial inspiratory airway resistance were obtained as previously described.[7 8] Reference values were obtained from previous work from this laboratory.[9] As some controversy exists about the validity of measurement of thoracic gas volume in wheezy individuals[10 11] specific airway resistance, the product of thoracic gas volume and initial inspiratory airways resistance, was used as a more reliable index of baseline lung function.[11 12]

The infants were then placed in an inflatable polythene jacket,[6] which extended from the shoulders to the upper thighs, with a cut away at the neck to avoid putting pressure on the trachea. Flow and its integral volume were measured using a heated screen pneumotachograph (diameter 19 mm and linear to 40 l/min) with accompanying flow transducer (Validyne MP45) attached to a facemask (Rendell Baker), which was sealed around the nose and mouth with silicone putty. By rapidly inflating the jacket at end inspiration to pressures of between 30 and 40 cm H_2O, partial expiratory flow volume curves were produced and measurements of peak expiratory flow rate from end inspiration and maximum flow at functional residual capacity ($\dot{V}$max FRC) were obtained as previously described.[6] Reference values were obtained from previous work.[6]

Bronchodilator administration

After six to eight baseline flow volume curves had been obtained 2·5 ml of a control solution of nebulised normal saline was administered, using a Turret nebuliser, the output of which was 2·1 ml/min at a flow rate of 6 l/min. After 10 minutes a further set of partial expiratory flow volume curves was obtained. Nebulised ipratropium bromide (250 mcg in 2·5 ml normal saline) was then administered and after 20 minutes repeat flow volume curves and measurements of thoracic gas volume and airways resistance were obtained. Eight patients awoke before the final set of plethysmographic measurements were completed, due to the duration of the procedures. One measurement of thoracic gas volume after and two airways resistance measurements before treatment with ipratropium bromide were technically invalid and not reported. There were therefore only eight complete sets of measurement of specific airways resistance available.

Statistical analysis. Paired *t* tests were used to assess the significance of the effect of ipratropium bromide on the lung function measurements obtained where paired data were available. Individual responsiveness to ipratropium bromide was assessed as a change that was outside the confidence limits for $\dot{V}$max FRC or airways resistance.[6 9]

Results

Baseline lung function data confirmed the presence of pronounced airways obstruction (Table 1). All infants had raised baseline values of airways resistance and specific airways resistance, the mean values for the group as a whole being 470% and 530% of the predicted reference values.[9] Baseline $\dot{V}$max FRC and peak expiratory flow rate when normalised for body length were 49% and 80% of their respective reference values.[6] After treatment with nebulised saline there was a small but insignificant drop in both peak expiratory flow rate and $\dot{V}$max FRC in the group as a whole (Table 2). Treatment with nebulised ipratropium bromide failed to improve the mean value of $\dot{V}$max FRC. Although the mean value of peak expiratory flow rate increased from 286 to 305 ml/sec, this increase failed to reach significance ($t=1·9$, $p=0·08$). In the eight infants who had complete sets of measurements of thoracic gas volume and airways resistance before and after treatment with ipratropium bromide there was a significant drop in the mean value of specific airways resistance from 14·7 to 8·7 cm H_2O/sec ($t=2·8$, $p=0·027$).

Most individual infants failed to show any significant change in $\dot{V}$max FRC or peak expiratory flow

Table 1 *Baseline lung function (% of reference value) in infants with wheeze*

	n	*Mean (SD)*
Thoracic gas volume	17	105 (47)
Airway resistance	15	470 (286)
Specific airway resistance	15	530 (417)
$\dot{V}$max FRC	17	49 (48)
Peak flow rate	17	80 (27)

$\dot{V}$max FRC=Maximum flow at functional residue capacity during forced expiration

Table 2 *Response to nebulised ipratropium bromide compared with saline in infants with wheeze*

	n	*Control*	*Saline*	*Ipratropium*
$\dot{V}$max FRC (ml/sec)	17	105 (114)	103 (107)	101 (110)
Peak expiratory flow rate (ml/sec)	17	286 (110)	281 (104)	305 (113)
Specific airways resistance (cm H_2O/sec)	8	14·7 (4·5)	—	8·7 (3·5)*

$\dot{V}$max FRC=Maximum flow at functional residue capacity
*Significantly different from pretreatment value ($p<0·05$) based on a paired *t* test, no other differences were significant

Table 3 *Individual responses to treatment with saline or ipratropium bromide in infants with wheeze*

	Saline			*Ipratropium*		
	Improved	*No change*	*Worse*	*Improved*	*No change*	*Worse*
Vmax FRC	2	13	2	2	14	1
Peak expiratory flow rate	—	15	2	5	12	—
Airways resistance	—	—	—	5	3	0

Vmax FRC=Maximum flow at functional residue capacity

rate after treatment with saline or ipratropium, although five (29%) had a significant increase in peak expiratory flow rate after ipratropium (Table 3). Of the eight patients who had complete sets of measurements of airways resistance before and after treatment with ipratropium, five had a significant reduction in resistance, while the others were unchanged. Three of these infants were among the five who had an increase in peak expiratory flow rate.

Discussion

To reassess the role of anticholinergic agents in the management of wheezy infants, we set out to determine the site of maximum effect of nebulised ipratropium bromide. We used specific airways resistance as an indicator of overall (largely upper and central) airways function and Vmax FRC as a measure of the peripheral airways response. There was significant reduction in specific airways resistance after treatment with ipratropium bromide, indicating an overall reduction in airways obstruction, but no improvement in the peripheral airways function as determined by Vmax FRC. Peak expiratory flow rate, generally thought to be influenced by large airways function, tended to improve after treatment with ipratropium.

These findings would tend to support the concept that in infants, as in adults, nebulised anticholinergic agents act predominantly on the large central airways,[3 4] with little effect on more peripheral airways function. Such agents may have more peripheral effect when administered intravenously.[3] Our results could also be explained by a reduction in nasal resistance, although we have no direct measurements. In adults, however, nebulised ipratropium has no direct effect on nasal airways resistance.[13]

Our results help explain the discrepancy between the reported alleviation of airways obstruction, as measured by an improvement in lung mechanics,[1] and the lack of appreciable clinical benefit shown in a clinical trial of ipratropium bromide in acutely wheezy infants.[2] Variables of airways function primarily used in this age group include pulmonary resistance and airways resistance, which are both measured during the inspiratory phase of tidal breathing

Upper and large, central airways contribute about 75% of the value of pulmonary or airways resistance in normal infants, so that an improvement in these variables after treatment with ipratropium bromide may occur without any improvement in peripheral airways function. In contrast, during an acute attack of wheeze, infants breathe actively, seeming to use forced expiration Under these circumstances, expiratory flow will be limited by peripheral airways function, and the appropriate laboratory measurement that most closely mimics the natural pattern of breathing is the forced expiratory flow volume curve, which was unaffected by ipratropium bromide.

Physiological considerations. There are other explanations for the discrepancy between the significantly improved airways resistance that we found and the lack of improvement in maximum flow at low lung volumes. Airway resistance measurements are determined by the calibre of the airways from nose to lung periphery. Maximum expiratory flow at any lung volume is determined by the elastic recoil pressure of the lungs, the density of the expired gas, and the calibre and compliance of the airways. The elastic recoil pressure of the lungs has been shown to remain constant after treatment with nebulised anticholinergic agents [3]

For a constant gas density, maximum flow is then determined by the calibre and compliance of the airways. Should an increase in calibre be equally matched by an increased compressibility of the peripheral flow limiting airways at low lung volumes, such that maximum flow remained constant, no increase in maximum flow at functional residual capacity would be detected, despite a reduction in airways resistance during quiet breathing. It seems unlikely, however, that these effects should be so equally matched as to show no change. It is more likely, as previously shown in adult subjects, that nebulised anticholinergic agents, in contrast to intravenous atropine, have minimal effect on peripheral structures in the lung.[3]

Another explanation for the lack of improvement in Vmax FRC could be a change in the absolute lung volume at functional residual capacity such that, if the lungs became less hyperinflated after ipratropium, Vmax FRC was being measured at a lower lung volume than before treatment Measurements of thoracic gas volume were made before and after treatment with ipratropium. In the 13 completed sets of measurements the mean (SD) values of thoracic gas volume were 199 (64) ml and 198 (62) ml, respectively Though measurements of thoracic volume are notoriously unreliable in wheezy individuals,[10 11] it seems unlikely from these results that a fall in absolute lung volume was masking a true improvement in peripheral airways function

Clinical implications and conclusions. Ipratropium bromide seemed to have its major effect on central or upper airways, as in older subjects. This may explain its limited clinical role as a bronchodilator agent in the presence of pronounced peripheral airways obstruction, as in bronchiolitis There seems little clinical or physiological support for the widespread use of nebulised ipratropium bromide in the management of wheezy infants, although it is possible that some individuals may obtain some benefit.

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Local production of rotavirus specific IgA in breast tissue and transfer to neonates

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SUMMARY Rotavirus specific IgA, secretory component, and IgG were measured by enzyme linked immunosorbent assay in 20 pairs of mothers and babies to estimate antibody transfer from the mother, particularly from breast milk to neonatal faeces. Colostrum contained high titres of specific IgA and secretory component, which decreased gradually. Faeces after breast feeding for three days showed detectable titres of IgA and secretory component, with further increases by seven days. There was a positive correlation between titres of secretory component in breast milk and in faeces. To clarify the mechanism of high anti-rotavirus activity in breast milk, ratios of rotavirus specific IgA in maternal serum samples to breast milk were calculated and compared with those that were herpes simplex virus specific. Significantly higher concentrations were obtained for the herpes simplex virus specific samples, indicating that anti-rotavirus IgA is selectively produced in breast tissue.

During the past decade rotaviruses have been shown to be a major cause of neonatal and infantile gastroenteritis throughout the world They still constitute a great threat to young children, causing morbidity as well as mortality, particularly in those in developing countries. Breast feeding has been shown to protect neonates and infants from various infections.[1] This protection extends to rotaviral gastroenteritis, at least to some extent, as lower incidences of viral diarrhoea have been found in breast fed infants.[2] Newborns and infants in general under 6 months of age have been shown to have mild or asymptomatic rotaviral infection [3]

Gut associated lymphoid tissue (as the local defence mechanism against this virus) consists of Peyer's patches and other lymphoid tissues in the intestine, including mesenteric lymph nodes. After antigenic stimulation in the gut primed B cells, particularly cells that produce IgA, can migrate from there to various sites of external secretions, such as breast tissue, to produce local antibody there [4] This study was undertaken to determine the reason for relative resistance to rotaviral gastroenteritis in the newborn period by estimating the antibody transfer from the mother and also to explore the role of maternal gut associated lymphoid tissue against neonatal rotavirus infection

Patients and methods

Preparation of antigen. For rotavirus antigen, human rotavirus strain Wa was grown and propagated in MA104 cells, then concentrated by precipitation with polyethylene glycol, and finally purified by sucrose gradient centrifugation.[5] Protein concentration of the extract was 800 µg/ml as estimated by the Lowry method. For herpes simplex virus antigen, the HF strain of the virus type I was propagated in Vero cells and purified by sucrose gradient centrifugation Protein concentration was estimated and diluted with carbonate buffer (pH 9·5) to obtain a final concentration of 2·5 µg/ml during use.

Samples. Breast milk, serum, and faecal samples were collected from 20 pairs of mothers and neonates. The mothers and babies were enrolled in the study at random according to delivery serials in the hospital, but very low birthweight babies and their mothers were excluded.

Samples of breast milk were collected three times: before beginning lactation and three days and seven days after lactation. These samples were first centrifuged at 2000 *g* for 10 minutes, and then upper lipid and lower cellular portions were discarded and recentrifuged at 4500 *g* for 30 minutes so that the middle portion could be collected.[6] Each mother had a serum sample taken before lactation, and each neonate had serum samples taken before breast feeding began and seven days after breast feeding had started. Three faecal samples were taken from each neonate, one before breast feeding and one three days and one seven days after breast feeding had begun The faecal samples were mixed with phosphate buffered saline, homogenised, and centrifuged at 10 000 revolutions per minute for 30 minutes at 4°C to collect the supernatant fluid. Latex agglutination tests were performed on the faecal samples by using Rotalex kit (Orion Diagnostica, Denmark) to exclude asymptomatic rotaviral infection during the study. All the faecal samples yielded negative results, indicating the absence of rotavirus

Enzyme linked immunosorbent assay. Immunolon microelisa plates (Dynatech, Virginia, United States) were used for measuring antibodies. IgA, secretory component, and IgG titres against rotavirus and herpes simplex virus were determined using the procedure we have reported previously[7] The rotavirus antigen was thawed and treated with sodium thiocyanate to increase its ability to attach to the solid phase[8] To exclude the possibility of non-specific reactions, antigen free plates were used as controls every time Peroxidase conjugated rabbit immunoglobulins to human secretory component (Dako, Copenhagen, Denmark) were used at dilutions of 1:200. Peroxidase conjugated, affinity purified, heavy chain specific goat antibodies to human IgA and IgG (Tago, California) were used at dilutions of 1:500 and 1 2000, respectively.

Results of the assay were expressed with reference to standard curves. The standard curves were prepared separately for secretory component, IgA, and IgG from several estimations of specific antibodies to twofold serial dilutions of different serum and colostral samples. Samples that had higher titres of antibodies were chosen as standards The antibody titres of samples were decided in terms of the dilutions (2^n) of standard samples, the optical density of which corresponded to that of the desired sample.

Results

Transfer of antibody from mother to neonate. Figure 1 shows the transplacental transfer and kinetics of rotavirus specific antibodies in the serum of the neonates All the maternal serum samples contained high titres of IgA ($2^{8\ 04}$) as well as of IgG ($2^{6\ 2}$). The IgG transfer ($2^{6\ 25}$) was almost in the same titre, whereas IgA transfer (2^{1-57}) was low Secretory component was not detectable in either maternal or neonatal serum samples

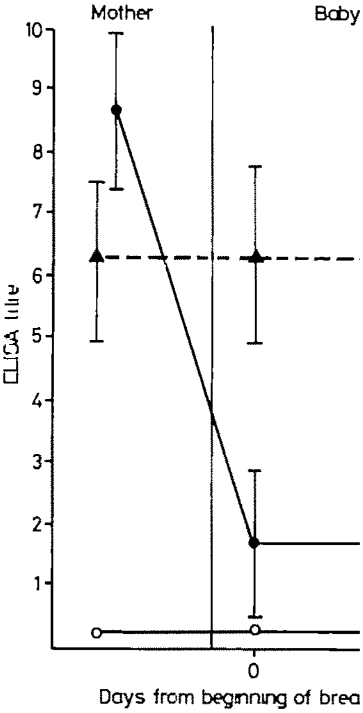

Fig 1 *Transplacental transfer and kine serum of rotavirus specific antibodies E immunosorbent assay titres of antibodie: IgG (250×2ⁿ) (▲- - - -▲), and secretc (100×2ⁿ) (○——○) expressed in compa standard curves Vertical lines indicate s*

The titres of rotavirus specific a milk are shown in Figure 2(a). Tit and secretory component ($2^{8\ 75}$) high concentrations in all colostral IgG titre ($2^{1\ 67}$) was low. All th showed a rapid decrease in the san days after lactation, with a gradua wards On the other hand, an neonatal faeces showed reverse t could not detect any antibody i (Fig 2(b)), titres of rotavirus speci secretory component ($2^{3\ 25}$) were d cant amounts in the samples taker breast feeding, which showed a (2^{6-25} and $2^{4\ 35}$, respectively) by day undetectable even after seven day ing A definite correlation betwee fic secretory component in breast n faeces was found (r=0·763) (Fig.

Ratios of serum IgA to breast r rotavirus and herpes simplex viru

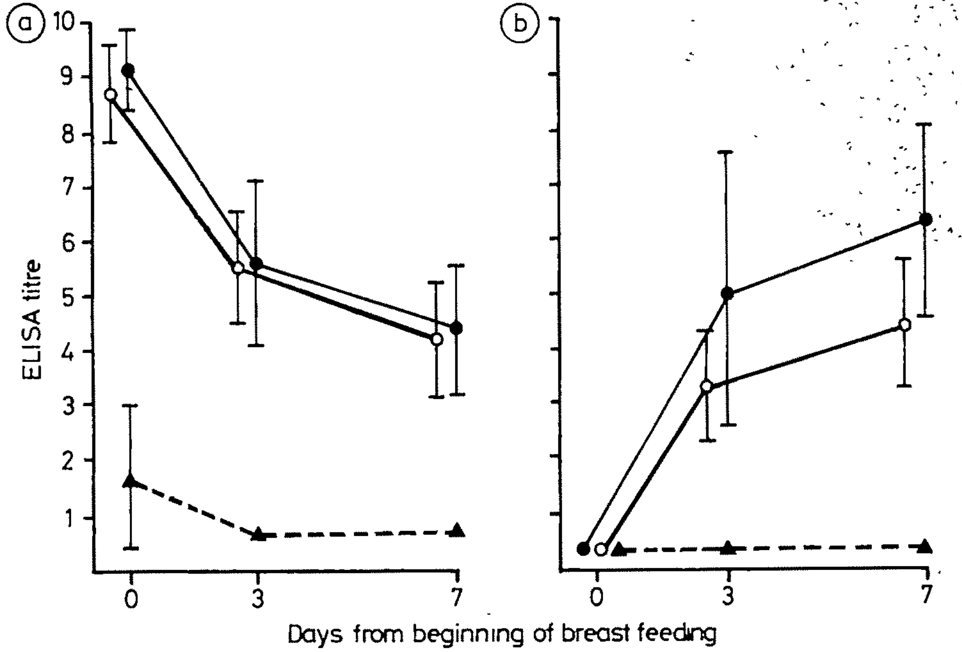

Fig. 2 *Rotavirus specific antibodies IgA (●——●), IgG (▲- - - -▲), and secretory component (○——○) in breast milk and baby's faeces. (a) Enzyme linked immunosorbent assay titres of antibodies IgA (1000×2ⁿ), IgG (40×2ⁿ), and secretory component (200×2ⁿ) in breast milk, (b) titres of antibodies IgA, IgG, and secretory component (100×2ⁿ) in baby's faeces Titres expressed in comparison with the standard curves Vertical lines indicate standard deviations.*

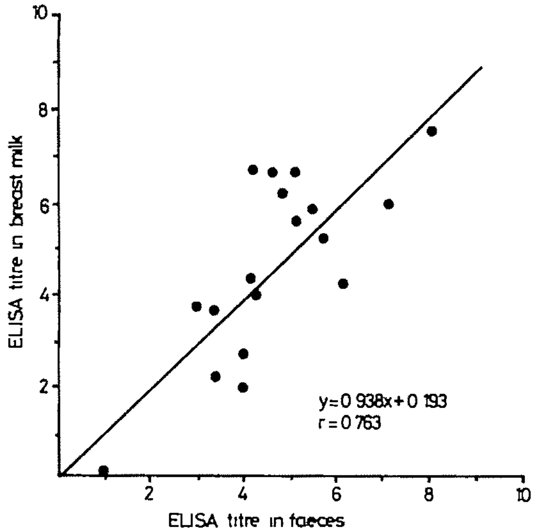

Fig. 3 *Correlation between rotavirus specific secretory component in breast milk and baby's faeces Enzyme linked immunosorbent assay titres in breast milk (200×2ⁿ) and faeces (100×2ⁿ) expressed in comparison with the standard curves*

reason for high titres of rotavirus specific IgA in breast milk, we compared the ratios of serum to milk titres (Table). For comparison, the ratios were estimated in the same manner for herpes simplex virus, which cannot replicate in the gut. There was a significant difference (Student's *t* test for paired groups) between the ratios of rotavirus specific IgA in maternal serum to breast milk and the herpes simplex virus specific ratios, the latter showing a higher value ($p<0·05$). The mean (SD) serum: breast milk ratio was 2·8 (2·1) for rotavirus and 4·5

Table *Mean (SD) ratios of serum to breast milk IgA titres against rotavirus and herpes simplex virus type I*

Virus	*ELISA titres of antiviral IgA (2ⁿ)*		*Ratio of ELISA titres (serum breast milk)*
	Serum†	*Breast milk‡*	
Rotavirus	8·7 (1·9)	5·9 (1·9)	2·8 (2·1) }*
Herpes simplex virus type I	7·0 (0·7)	2·5 (1·6)	4·5 (1·7) }

ELISA=Enzyme linked immunosorbent assay
*p<0·05
†Maternal serum at 250 times' dilution
‡At 1000 times' dilution

(1-7) for herpes simplex virus Thus rotavirus specific IgA in breast milk was significantly higher, indicating that the antibody is locally synthesised in breast tissue.

Discussion

Our results show that transplacental transfer of rotavirus specific IgA and IgG corresponds to the general antibody transfer as shown by other studies.[9] Iyenger *et al* have shown that there is preferential transfer of IgG in comparison with IgA and IgM.[10] We have observed that rotavirus specific IgG transfer is also preferential

As far as the fate of rotavirus specific antibodies in breast milk fed to neonates is concerned, most of the IgA and secretory component were excreted in the faeces of the neonates. Before or during the process of excretion, these antibodies probably form a covering over the microvilli of the upper intestinal tract, giving passive protection, as shown by Nagura *et al* in the gastrointestinal tract of rats.[11] Rotavirus specific IgA and secretory component detected in neonatal faeces after breast feeding are thought to be derived entirely from milk as no rotaviral outbreak occurred during the study and asymptomatic infections were also ruled out by negative latex agglutination tests in the faecal samples Although the breast milk samples showed more diminished titres of antibodies than colostrum samples, faecal samples showed increased titres of IgA and secretory component. This is possibly due to the fact that the amount of milk taken by the neonate increased day by day, thus increasing the total antibody intake

From our study, we have seen that all the mothers had high titres of rotavirus specific antibodies in breast milk and serum. This indicates that all of them had previous rotavirus infection, which corresponds to other studies, indicating the ubiquitous nature of the rotavirus and rotavirus specific antibodies.[12] Titres of rotavirus specific IgA and secretory component in the colostral samples were much higher than in the serum samples. The IgA in breast milk is believed to be mainly secretory IgA in nature This points us to the assumption that anti-rotavirus antibody is produced locally in the breast tissue by stimulation of IgA producing cells that have migrated from the gut associated lymphoid tissue because direct infection of the mammary tissue with rotavirus does not occur. Antigens in the gut lumen are thought to stimulate the precommitted (IgA producing) lymphoid cells there, and some of these cells migrate to external secretory tissues—for example, breast tissue—for production of antibody.[4] Comparatively lower titres of breast milk antibody against herpes simplex virus, which cannot multiply in the gut, also support our hypothesis Our previous study showed that there is anamnestic response for IgA production in the gut after reinfection with rotavirus.[7] By some mechanisms, the reinfection in the gut may also cause production of specific secretory IgA in breast tissue.

Our study has the limitation that we have observed antibody titres for only seven days after lactation and after the start of breast feeding. But it suggests that if the initial rotavirus specific antibodies are high then the neonate may get passive protection in the intestinal tract for prolonged periods of breast feeding. Local antibodies to rotaviruses in the gut rather than systemic antibody are thought to be of primary importance in protection from infection. Animal studies have indicated that rotavirus infection occurs when the viral antigen titre exceeds the colostral neutralising antibody titre [13] The role of maternal breast milk IgA, in supplying local IgA to the gut in the early neonatal period, is immense and hence the role of maternal gut associated lymphoid tissue is indirectly also important.

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Fifty years ago

Plasma phosphatase in the diagnosis of rickets

Noah Morris, Mary M Stevenson, Olive D Peden, and Jean M D Small (Glasgow)—Arch Dis Child 1937,**12**:45–58

Plasma phosphatase was measured in 506 children in the first two years of life, all of whom had manifest rickets or might have been deficient in vitamin D Raised values were found in 84% of cases with clinical or *x* ray evidence of rickets, and a high plasma phosphatase value was more often associated with rickets than a reduced serum phosphorus concentration. In general the phosphatase activity ran parallel with the degree of rickets, but the correlation was not a close one While healing of the rickets was associated with a fall in the phosphatase activity, in no case did this precede radiological evidence of healing In fact, the initiation of antirachitic therapy was occasionally followed by a transient rise in the plasma phosphatase. The authors postulated that the rare occurrence of a normal phosphatase activity with signs of active rickets might be explained on the assumption that growth had temporarily stopped, while the presence of a high plasma phosphatase activity in the absence of evidence of rickets could be attributed to an insufficient supply of calcium to meet the demands of active bone cells. Rise in the plasma phosphatase activity was considered to be an earlier manifestation of rickets than any provided by clinical or radiological examination and also a more sensitive test than the fall in serum phosphorus or the calcium-phosphorus product

Comment. This was one of the earliest reports on the value of the plasma phosphatase activity in the diagnosis of early rickets. The conclusion that the alkaline phosphatase activity rises before there are radiological changes may be erroneous, and the earliest sign of rickets is probably loss of radiological definition of the metaphyseal ends of long bones such as the radius and ulna. Interpretation of minor *x* ray changes is open to the criticism, however, that it is highly subjective The much more recent ability to measure the plasma 25-hydroxycholecalciferol concentration probably supplies us with a more reliable index of the vitamin D state of a community

(Noah Morris was biochemist to the Royal Hospital for Sick Children in Glasgow He was responsible for introducing a series of young graduates to the excitements of research in paediatrics, two of these later occupied chairs in paediatrics and one a chair in pathology Shortly after publication of this paper Morris was appointed to the Chair of Materia Medica in Glasgow and he devoted the rest of his too short life to clinical practice and research in adult medicine His book, 'Acidosis and alkalosis', written in conjunction with Professor Stanley Graham, was a minor classic in the 1930s when few British paediatricians appreciated the value of biochemistry to the clinician)

J H HUTCHISON

Archives of Disease in Childhood, 1987, **62,** 406–420

Short reports

Oral candida: is dummy carriage the culprit?

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SUMMARY Oral candida in subjects who sucked dummies was almost double that of controls. Although the carriage of *Candida albicans* on silicone dummies was significantly reduced compared with latex dummies, oral colonisation was unaffected, suggesting that dummy carriage is not the cause of the observed increase.

The use of dummies has recently been shown to be associated with a higher incidence of oral candidiasis and persistent colonisation in acutely ill infants, possibly because of carriage on the dummy.[1]

Dummies are usually manufactured from latex rubber, but a dummy made of silicone rubber has recently become available. We wondered, therefore, whether the relation between dummy usage and oral candida was also true of healthy children and whether the smoother surface of a silicone dummy would be associated with less adhesion of candida and reduced oral colonisation.

Subjects and methods

Subjects. Ninety five healthy children aged 1–24 months, attending a well baby clinic, were entered into the study. Those with symptomatic oral candidiasis or other forms of oral abnormality, or both, were excluded. Informed parental consent and research ethical approval were obtained.

Methods. All those who did not use dummies were allocated to group A (controls); those who did use dummies were randomly allocated to either group B (continued use of a new latex dummy throughout the study, n=26) or group C (changed to a new silicone dummy at the beginning of the study, n=26). Where appropriate, mothers were issued with two dummies and instructions to carry on with their usual practice of dummy care. Oral examination was performed, and swabs taken from the tongue, hard palate, and dummies at the start of the study and after eight and 16 weeks. Swabs used for dummy culture were moistened in sterile saline solution and rubbed over the entire surface of the dummy before transport to the Children's Hospital, Birmingham. Swabs were plated on Sabouraud's agar (dextrose) and incubated at 37°C for 48 hours. Yeast colonies were classified on the basis of sucrose fermentation, germ tube production, and assimilation reactions using the API 20 C Auxanogramme. Scanning electronmicroscopy was performed on representative dummies from each group.

Statistical analyses were performed using the χ^2 test.

Results

None of the children developed oral candidiasis. The overall incidence of colonisation with candida in those who used dummies at the start of the study was almost twice that of controls (52% *v* 28%, $p<0{\cdot}02$); a similar difference was observed for colonisation by *Candida albicans* alone (31% *v* 12%, $p<0{\cdot}05$).

After eight weeks 26% of the controls and 62% of those using latex dummies were colonised by *Candida* spp ($p<0{\cdot}01$). Although only 46% of the group using silicone dummies were now colonised by *Candida* spp, this difference was not significantly lower than that of the group using latex dummies. Similarly, the incidence of colonisation by *C. albicans* alone did not differ significantly in the groups using silicone and latex dummies (23% *v* 31%, respectively).

Although after 16 weeks the overall growth of *Candida* spp was significantly increased in the group using silicone dummies compared with the group using latex dummies, the incidence of colonisation with *C. albicans* was again unchanged. By this stage of the study, however, 50% of the group who had started with latex dummies only were using both dummies whereas 78% of the group using silicone

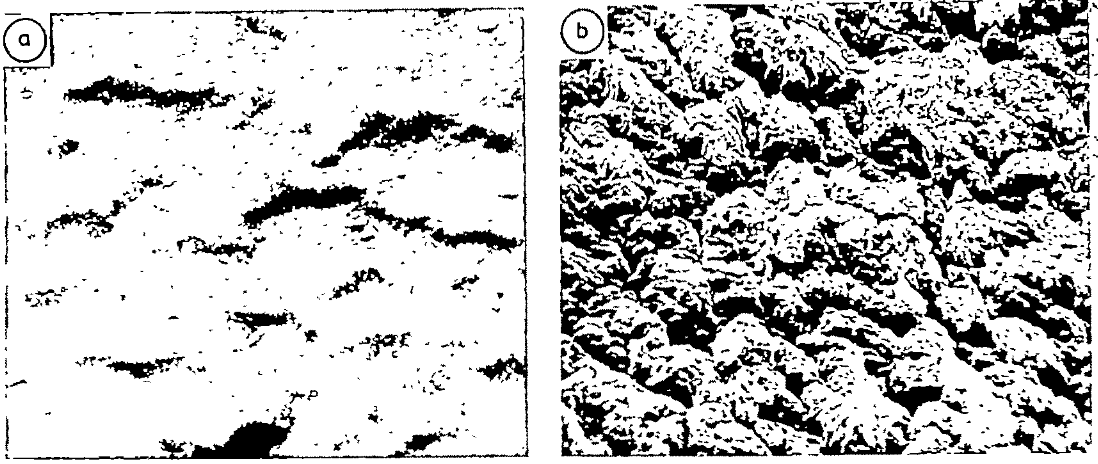

Figure *(a) Scanning electronmicrograph of a representative silicone rubber dummy at the end of a 16 week period, depicting the almost unchanged smooth surface of the dummy. (b) Scanning electronmicrograph of a representative latex rubber dummy at the end of a 16 week period, showing the markedly fissured surface of the dummy*

dummies were still using only one ($p<0\cdot05$), contrary to our initial request. There seemed to be no other difference in dummy care between groups.

To establish the role of carriage of *C. albicans* on the dummy in oral colonisation, the proportion of children with mouth cultures that were positive for *C. albicans* who also had cultures on their dummies—that is, carriage rate on dummies—was studied. Although there was no difference in the rate of oral *C. albicans* colonisation between the two groups, the carriage rate of *C. albicans* on the silicone dummies (22%) was significantly less than on the latex dummies (75%) ($p<0\cdot05$)

In contrast with previous studies, a wide variety of non-pathogenic *Candida* spp were isolated and in total slightly exceeded those of *C. albicans*—namely, *C. albicans* 46% of all isolates, *C. parapsilosis* 37%, *C lusitaniae* 8%, *C. guilliermondi* 68%, *Torulopsis candida* 2%, and *C. tropicalis* 1%.

Scanning electronmicrographs (Figure) showed that the initial smooth appearance of both dummies was almost unchanged in the silicone dummies, whereas the latex dummies had become markedly fissured.

Discussion

The twofold increase in oral candida colonisation seen in our healthy population of dummy users confirms the previous observations of Manning *et al* in acutely ill infants.[1] Such an increase may be related to the presence of foreign bodies in the mouth, similarly observed among denture wearers.[2] Moreover, illness seems to predispose to colonisation with *C. albicans* and clinical candidiasis, for the overall incidence in ill children was higher than in our healthy population.

Although the rates of colonisation with *C. albicans* were unchanged at the end of the study, the use of a silicone dummy was associated with a lower rate of carriage of *C. albicans* on the dummy. The finding of pronounced differences in surface morphology of the two types of dummies may be important (Figure).

These observations therefore suggest that the increased predisposition to oral colonisation with *C. albicans* that occurs with dummy usage does not happen simply from dummy carriage but results from a more subtle disturbance in the ecosystem of the mouth, the nature of which remains speculative.

The clinical importance of increased colonisation with species other than *C. albicans* in the dummy sucking group is difficult to assess Although these species are usually considered to be non-pathogenic to man, opportunistic infections with *C. lusitaniae, C. guilliermondii,* and *C tropicalis* have been described.[3-5] These observations may therefore be relevant in the immunocompromised dummy user who is undergoing attempted gut sterilisation.

The British Standards Institute has expressed its concern over the inadequacy of the current standard on babies' dummies, BS5239, particularly in relation to the spike test. After adverse publicity the manufacturers of silicone dummies have voluntarily withdrawn their products from sale pending revision to the safety standard, which is expected in early 1987

We would like to thank D Healing and M Oud for their invaluable help with the microbiological procedures and Dr S Knutton for preparing the electronmicrographs The dummies were kindly supplied by Pur L S R Baby Products (UK) Limited.

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Mechanism of erroneous Dextrostix readings

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SUMMARY The mechanism of hyper-reactivity of the Dextrostix system when contaminated with alcoholic skin cleaning agents was investigated. When sodium fluoride was supplied to block glucose oxidase activity and hydrogen peroxide was exogenously provided benzidine peroxidation could be preferentially studied Benzidine hydrochloride was the most likely site of the hyper-reaction.

Repeated measurement of blood sugar is especially important in newborn infants who are susceptible to hypo- and hyperglycaemia. Dextrostix (Ames Co, United States) is a blood sugar measuring system that uses dry chemistry and is often used in intensive care medicine because of its accuracy and convenience.[1] The system consists of two enzymatic steps:

$$\text{Glucose}+2H_2O \xrightarrow[O_2]{\text{glucose oxidase}} 2H_2O_2+\text{glucuronic acid}$$

$$2H_2O_2+\text{Benzidine} \xrightarrow{\text{peroxidase}} 2H_2O+\text{ox-benzidine}$$

where ox-benzidine is the oxidised form of benzidine. These reactions are highly dependent on the quantity of glucose. The system does not respond to reduced sugars, and substances such as lactose, fructose, galactose, glutathione, ascorbic acid, uric acid, creatinine, amino acid, and glycolytic intermediate in its routine clinical use. Haemolysis, bilirubin, and the addition of glycolysis blocking agents, such as ascorbic acid, are known to interfere with the system [2 3]

Isopropyl alcohol, often used during the preparation of the blood sampling site, causes an erroneously high glucose reading as measured by Dextrostix.[4 5] In the present study we investigated the mechanism of serum glucose measurement when the Dextrostix system was contaminated with various alcoholic agents and reiterate the potential problems of interpreting such factitious results.

Methods

To determine the site of hyper-reaction caused by alcohol in the Dextrostix system, 0·5 ml of isotonic saline sodium fluoride solution was used to block glucose oxidase activity, the first step of the system, and 0·5 ml of 1% hydrogen peroxide (first grade) then added to the tip of Dextrostix. Blood sugar measurements were performed by routine technique except for pretreatment with these agents. The effect of alcohol on dye was analysed using two other systems that also measure pure glucose using the same enzymes but different dyes. The tip of a Reflomat system (Yamanouchi Co, Japan), which contains propylcarbazol and toluidine as dye, and the Seralyzer system (Ames Co), which contains tri-methylbenzidine, were directly soaked and contaminated to 45% isopropyl alcohol. Fifty per cent isopropyl alcohol, 50% *N*-propanol, and 50% ethylalcohol, used in the analysis of other alcoholic agents to the Dextrostix system, were all of analytical reagent grade. 0·5ml Of artificially developed serum, packaged with Dextrostix Dextrometer system, was used as control serum

Table 1 *Effect of alcohol on Dextrostix reading*

	Mean (SD) blood sugar (mmol/l) (n=5)
Serum	8·19 (0·34)
Serum+sodium fluoride	1·65 (0·26)
Serum+sodium fluoride+45% isopropyl alcohol	1·71 (0·27)
Serum+sodium fluoride+hydrogen peroxide	8·07 (1·09)
Serum+sodium fluoride+hydrogen peroxide+ 45% isopropyl alcohol	>22·20

Results

As shown in Table 1, pretreatment with sodium fluoride significantly blocked the reaction of the first step and decreased the blood sugar readings from 8·19 mmol/l to the base concentration of 1·65 mmol/l. No change in blood sugar reading was found after the addition of 45% isopropyl alcohol, indicating that alcohol has no effect on the recovery of glucose oxidase activity.

Hydrogen peroxide significantly increased the blood sugar concentration to the initial value, where the first step was equally blocked by sodium fluoride. Subsequently, a profound increase of blood sugar was observed by the addition of 45% isopropyl alcohol.

Table 2 summarises blood sugar readings when control serum samples were applied to three different systems. An increase of 111% in blood sugar measurements using the Dextrostix system was found by the addition of 45% isopropyl alcohol, while a 9% increase and a 32% decrease were observed when measured by the Reflomat and the Seralyzer systems, respectively.

Fifty per cent isopropyl alcohol, 50% *N*-propanol, and 50% ethylalcohol also gave significantly high readings (mean (SD)) of 21·13 (1·09) mmol/l, 19·01 (0·36) mmol/l, and 18·58 (1·49) mmol/l, respectively, while the control serum showed only 6·99 (0·55) mmol/l (n=5 in all four cases)

Discussion

The Dextrostix system was confirmed as giving erroneously high glucose readings when contaminated with 45% isopropyl alcohol, one of the skin cleaning agents routinely used with capillary blood sampling. Alcohol probably reacts on the second step of the Dextrostix system.

From the facts that toluidine is one of the components of both the Dextrostix and Reflomat systems and that a significant decrease in blood glucose reading was found when tri-methylbenzidine was used as a dye, benzidine hydrochloride would be the most likely site of the hyper-reaction. Other alcoholic agents also gave erroneously high readings, indicating that alcohol is the main cause of the reaction. The enhanced colour development is probably due to increased solubility of the reduced indicator dyes A 32% decrease after contamination of the Seralyzer system with isopropyl alcohol should be elucidated, however, by further studies.

It is also important to note that the colour of the tip does not change at all by contamination of alcohol before application of blood samples. This is especially important as the contamination cannot be judged from the colour change or even from the glucose reading by the system.

The results indicate that the Dextrostix tip must be kept away from the alcohol pad, and repeated measurement is recommended when unexpectedly high or low readings are observed.

Table 2 *Effect of alcohol on blood sugar determination*

System	*Dye*	*Mean (SD) blood sugar (mmol/l)*		*% Increase*
		Control (n=5)	*Contaminated with 45% isopropyl alcohol (n=5)*	
Dextrostix	Benzidine hydrochloride+toluidine	3·89 (0·11)	8·21 (0·22)	111
Reflomat	Propylcarbazol+toluidine	7·78 (0·17)	8·45 (0·10)	9
Seralyzer	Tri-methylbenzidine	5·38 (0·12)	3·66 (0·13)	−32

The authors thank Dr Jay Roberts for his careful review of the manuscript

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Chromosomes of metastatic retinoblastoma

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SUMMARY Chromosomal abnormalities were detected in the bone marrow of a girl with disseminated retinoblastoma. One of these abnormalities, i(6p), is characteristic of primary retinoblastoma and its presence confirmed the diagnosis of bone marrow infiltration with retinoblastoma. This approach could be extended to study other tumours of childhood.

Characteristic chromosomal abnormalities have been described in primary retinoblastoma cells.[1–4] The availability of fresh tumour tissue for such investigations, however, is limited, not least by the traditional practice of immediate fixation of the enucleated eye so that accurate staging of the tumour can be achieved. Disseminated retinoblastoma with involvement of the bone marrow is rare. Nevertheless, when this pattern of disease occurs it provides the opportunity to examine directly the karyotype of the tumour cells.

Monoclonal antibodies are of value in determining the tissue of origin of metastatic disease, and specific cytogenetic abnormalities may also be of help. We report the karyotypic abnormalities of metastatic cells in a child with retinoblastoma who developed bone marrow infiltration.

Case report

A girl, aged 2 years and 5 months whose unilateral retinoblastoma had been enucleated one year previously, presented with three hard lumps on her head. There was no family history of retinoblastoma and her sibling's eyes were normal. Apart from these lumps and the enucleation, physical examination, including that of the opposite eye, yielded entirely normal results. A bone scan showed areas of increased uptake in the skull. A blood count showed haemoglobin 9·3 g/dl, white blood cell count $6 \cdot 7 \times 10^9$/l (30% neutrophils, 65% lymphocytes, and 5% monocytes), and platelets 90×10^9/l. Ultrasound examination of her abdomen produced normal results. There were no intracranial abnormalities on computed tomography of her head.

Biopsy examination of one of the lumps on her head showed a primitive round cell tumour with small darkly staining cells and limited eosinophilic cytoplasm. In areas there were attempts at rosette formation. Examination of her bone marrow showed widespread infiltration with non-haemopoietic malignant cells, which resembled disseminated neuroblastoma. The malignant cells reacted with the monoclonal antibody UJ13A, which detects cells of neuroectodermal origin.[5] Urinary excretion of vanillylmandelic acid was normal. The cerebrospinal fluid did not contain malignant cells. A diagnosis of disseminated retinoblastoma with bone marrow involvement was made. Peripheral blood esterase D activity was normal. She was treated with vincristine, cis-platinum, teniposide, and cyclophosphamide (OPEC). Although there was initial clearing of malignant cells from the bone marrow, she died nine months later from recurrent disease.

Chromosome analysis of bone marrow derived metaphases showed two cell lines, three cells had an apparently normal 46,XX karyotype and three represented an abnormal clone with a modal num-

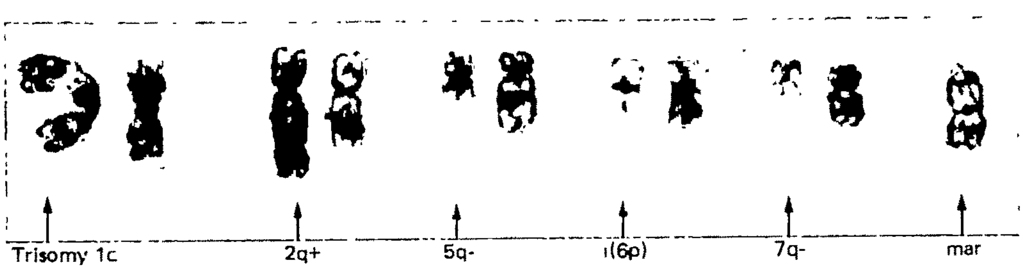

Figure *Partial karyotype, showing trisomy 1q, 2q+, 5q−, i(6p), 7q−, and a marker chromosome* ber of 45 chromosomes. Consistent anomalies were trisomy 1q, 2q+, 5q−, 7q−, an unidentified marker chromosome, and tetrasomy of the short arm of chromosome 6, manifest as an additional isochromosome, i(6p) (Figure). Some random chromosome loss was evident.

Discussion

Though it only rarely occurs, retinoblastoma is known to disseminate to the bone marrow. The occurrence of the malignant cells in the bone marrow and their reactivity with UJ13A were highly suggestive of a neuroectodermal origin. Second primary tumours have been described in patients with hereditary bilateral forms of retinoblastoma, although they usually occur much later than this. Neuroblastoma, primitive neuroectodermal tumour, and medulloblastoma, also derived from neuroectodermal tissue, are not recognised, however, as characteristic second malignant neoplasms in these patients. In addition, the absence of either an intracranial mass lesion or an abdominal tumour and a normal urinary excretion of vanillylmandelic acid made a diagnosis of medulloblastoma or neuroblastoma unlikely. Primitive neuroectodermal tumours, unlike neuroblastoma, rarely involve the bone marrow. The evidence that this disseminated tumour was retinoblastoma is compelling.

The presence of large numbers of dividing retinoblastoma cells in such a readily accessible tissue provided the rare opportunity to obtain direct chromosome preparations and compare any abnormalities with reports of those obtained from fresh primary tumour tissue.

This is only the second report of the karyotypic abnormalities of metastatic retinoblastoma. Benedict *et al* described trisomy 1q, i(6p), and an interstitial deletion of 13q in cells from a rib metastasis [1] These three are the most common abnormalities in cases of primary retinoblastomas,[1–4] two of which, i(6p) and trisomy 1q, were found in the metastatic cells in our patient. The additional abnormalities 2q+, 5q−, 7q−, and the marker chromosome may reflect more malignant growth characteristics of the metastatic cells of this tumour. The presence of two macroscopically normal chromosomes 13 is consistent with a sporadic, non-hereditary form of retinoblastoma, which is supported by the normal esterase D activity [6]

Although trisomy 1q is not specific for retinoblastoma, the similarities between the chromosomal abnormalities in the metastatic cells in our patient and those described in primary tumours, particularly the presence of i(6p), encourages the use of cytogenetic investigations to confirm the identity of metastatic deposits in this disease. This case illustrates the relative ease with which such information can be obtained. Clearly, this approach could be extended to the study of other tumours of childhood.

We thank Dr John Cowell, Insitute of Child Health, for determining esterase-D activity in the peripheral blood, Dr John Kemshead for examining the malignant cells with a panel of monoclonal antibodies, and the North of England Children's Cancer Research Fund

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Nedocromil sodium and exercise induced asthma

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SUMMARY Serial exercise tests were carried out by 12 children with asthma on two study days. After a control exercise test either nedocromil sodium 4 mg or placebo were given double blind by metered dose inhaler. Highly significant inhibition of exercise induced asthma occurred after nedocromil, lasting for over two hours.

Nedocromil sodium (Tilade) is a new anti-asthma drug that has selective mucosal mast cell stabilising properties.[1] In single dose human studies nedocromil has been shown to protect against exercise induced asthma,[2] while in clinical studies, in which it has been administered four times a day for one month, improvements have been shown in the control of adult asthma.[3] There are no published data in children.

Exercise induced asthma has been used as a provocation test for a number of years to assess the relative efficacy and duration of action of different drugs.[4] In this study the protective effect of inhaled nedocromil sodium on exercise induced asthma was studied in a double blind, placebo controlled manner in a group of children with asthma.

Patients and methods

Twelve children with asthma were studied. There were nine boys and three girls, all well known to our asthma clinic, whose ages ranged from 8 to 15 years (mean 13·9 years). All were skilled in the use of metered dose inhalers and each had a history of exercise induced asthma. Sodium cromoglycate, theophylline, and beta agonists were stopped 12 hours before each test, but they were allowed to have treatment with steroids.

The forced expiratory volume in one second (FEV_1) and forced vital capacity were measured using a rolling seal spirometer (Ohio) before exercise. Exercise testing consisted of steady state running on an inclined treadmill at an inclination of 12% (10% if the baseline FEV_1 was less than 60% predicted) for six minutes. The speed of the treadmill was such that the patient's pulse rate at the end of the exercise period was at least 170 beats a minute. The same setting and duration was used for each test in any one patient. FEV_1 was measured before and after exercise and the severity of exercise induced asthma was defined as the ratio of maximum fall in FEV_1 to the pre-exercise value expressed as a percentage.

There were two study days within one week. On each day a baseline exercise test was carried out. Ninety minutes after the start of the first test two puffs of either placebo or nedocromil (2 mg/puff) were administered double blind, using a metered dose inhaler. Lung function recordings were made before and after treatment. Three further exercise tests were then carried out on each of the two days 30, 150, and 270 minutes after treatment—that is, two, four, and six hours after the baseline exercise test. Paired *t* tests were used for comparisons between the mean level of exercise induced asthma at various times after challenge in the two study days. The degree of protection against exercise induced asthma was calculated after administration of nedocromil for each post-dose test as the difference between the baseline test and the post-dose test, expressed as a proportion (%) of the baseline value.

Results

The initial spirometric values were similar on the two study days. Nedocromil had no significant effect on these values over the 30 minute interval between administration and the succeeding exercise test. Towards the end of the control day, however, the FEV_1 was minimally, though statistically, lower than on the active study day. Before the fourth exercise test the mean difference in FEV_1 between the active and control studies was 0·21 l (9·5%) (Figure).

The exercise tests revealed two important effects. Firstly, analysis of variance was used to show that there was a significant decline in the severity of exercise induced asthma during the course of the study days, independent of treatment ($p<0{\cdot}001$). Secondly, treatment with nedocromil had an additional significant overall effect on the level of exercise induced asthma ($p<0{\cdot}001$). The difference was significant at 30 and 150 minutes and insignificant at 270 minutes (Figure).

Individual responses to nedocromil were determined using the protection index. Protection of at

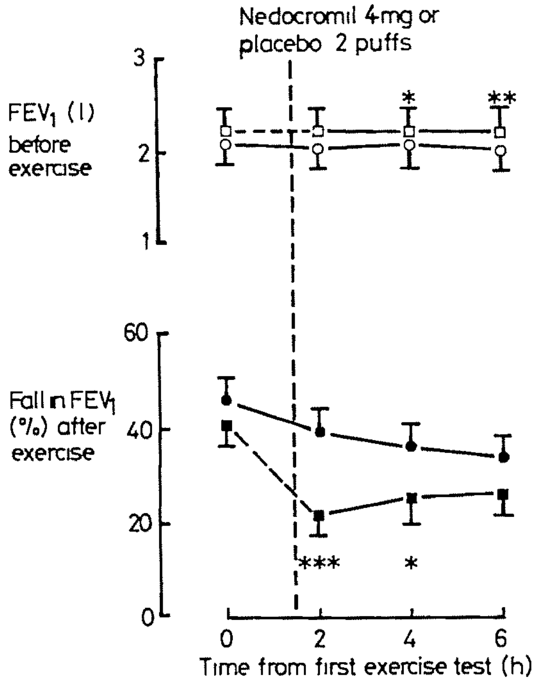

Figure *Results of the four exercise tests carried out before and after administration of nedocromil (squares) or placebo (circles) as measured by forced expiratory volume in one second (FEV$_1$). The treatments were administered 30 minutes before the start of the second test on each study day*

Results of paired *t* tests $^*p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$

least 40% was achieved in eight of the 12 children 30 minutes after administration. The protection declined with time.

Discussion

Although no direct comparison was made, in the 4 mg dose used, the effect of nedocromil on exercise induced asthma in children seems to be similar to that of sodium cromoglycate, both in the overall degree of protection and its duration.[4] As with cromoglycate given in the normal dosage there was no obvious change in pre-exercise spirometry after administration of the drug. After repeated exercise challenges on the two study days, however, there was a steady decline in FEV$_1$ on the placebo compared with the active treatment. Thus there was both short term protection against exercise induced asthma and longer term protection against the additive effects on lung function of repeated exercise.

The exercise tests were performed under ambient laboratory conditions. The exercise load was constant for each child for all eight exercise tests. Although it may be possible to increase the response to exercise by providing subfreezing or dry air during exercise, the overall response to the first (control) test on each study day suggests that the exercise stimulus was quite adequate. Only one child had a fall in FEV$_1$ of less than 25% on either control test.

In spite of the randomisation, the mean difference in exercise induced asthma before the control tests on the nedocromil and placebo test days was surprisingly large but not significant. We have no explanation for this difference other than random variation in a small population.

The mechanism by which nedocromil protects against induced bronchoconstriction has still to be understood in man. In the monkey, however, it can prevent release of histamine from anti-IgE stimulated bronchoalveolar lavage cells, which contain a high proportion of mucosal mast cells.[1] The evidence for two subpopulations of mast cells in man (the so called 'mucosal' and 'connective tissue' populations) is controversial. If nedocromil is selectively more active against mucosal mast cells it may represent an important advance in treatment of asthma over other agents whose presumed action is also on sensitised cells. As previously noted, however, the search for mast cell stabilising drugs has not led in general to major advances in the management of asthma.

The use of exercise tests for screening in new preparations for asthma has had a long history. The little clinical data that exist suggest that protection against exercise induced asthma in childhood may correlate with the outcome of long term treatment.[5]

If there is a dose-effect relation for nedocromil then a glance at the Figure suggests that the 4 mg dose should be increased. By increasing the dose, both the degree and duration of protection may be improved. Nedocromil could provide an important therapeutic advance in the management of childhood asthma.

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Management of asthma in schools

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SUMMARY A questionnaire on asthma in schools was circulated to 291 Nottingham schools. The response rate was 91%. Three areas of concern were identified: are schools aware of all their asthmatic pupils; should children have more access to their medications in school; and do teachers need more guidance in supervising illnesses.

Asthma is the most common chronic disease of childhood. It is associated with school absenteeism[1-3] and reduced participation in school activities and games.[1 2] Modern treatment of asthma is based on inhaled drugs administered from pressurised aerosols and dry powder inhalers. These can be safely self administered by virtually all children of school age,[4] and when used appropriately symptoms of asthma and absences from school are reduced.[3]

The management of asthma in schools and the role that teachers assume in this has not been described previously, despite the fact that children spend much of their time in school. We have looked into the awareness of asthma in schools and the policies adopted towards medications used to treat asthma to see whether there are specific problems for either teachers or children.

Methods and results

A questionnaire was posted to headteachers of 245 primary and 46 secondary state schools in the Nottingham area. The questionnaire asked how many pupils had asthma and how the schools were notified of this. Headteachers were questioned on their policy towards the administration and supervision of asthma medications and whether teachers had received instruction in the supervision of asthma or other childhood illnesses. Teachers were asked if they had experienced any particular problems when teaching children with asthma. Permission for the survey was granted by the local director of education and the city hospital ethical committee.

The questionnaire was returned by 92% of primary and 87% of secondary schools. The number of pupils known to have asthma ranged from 0 to 12% (mean 3·6%) in primary schools and from 1 to 6% (mean 2·9%) in secondary schools. The reported prevalence of asthma did not vary according to the size of the schools.

The majority of both primary and secondary schools were alerted to the fact that pupils had asthma by their parents (Table), usually verbally—

Table *Results of questionnaire on asthma management in Nottingham schools*

Question	*Response*	*School (response as a %)*	
		Primary	*Secondary*
How would you be informed if a child had asthma when he first joins the school?	Verbal report from parent	73	61
	Questionnaire to parent	22	34
	Previous school records	19	73
	School health service	5	22
How would you be informed if a child developed asthma later?	Parents	91	88
	School health service	31	42
	Pupil	1	15
	General practitioner/hospital	3	11
Who is responsible for supervising the needs of children with asthma?	Class teacher	80	35
	Head teacher	36	2
	Senior teacher	NA	39
	Pastoral staff	NA	15
	School nurse	5	59
	Nursery nurse	14	NA
Management of inhalers	Children keep	10	51
	Children hand in	65	10
	Children keep or hand in according to child	25	39

NA=Not applicable

for example, during parent's evenings. Roughly one quarter of schools asked parents for details of any health problems on an admission form Secondary schools also used records from the child's previous school.

The responsibility for supervising children with asthma lay predominantly with the teaching staff in primary schools, while in secondary schools the school nurse provided an additional source of support. The policy on whether inhalers should be handed in or not varied considerably In most primary (65%) and some secondary schools (10%) children were required to hand in their inhalers to the school office or class teacher and then to use them under supervision when necessary or at specific times during the day Children were allowed to keep and administer their inhalers themselves in 10% of primary and 50% of secondary schools. The remaining schools had a flexible approach and adapted to the individual child.

Only 8% of primary and 15% of secondary schools reported that teachers had received any instruction in the management of health problems. This information was often gained from voluntary first aid or health education courses and so was not necessarily specific to children. Many schools (40%) said that teachers were worried about their lack of preparation to cope with an attack of asthma and in some instances about the lack of suitable facilities for such an event. They also thought that they were not always aware if a child had asthma. Primary schoolteachers were concerned about the extra time needed to ensure that children took their medications Loss of schooling and reduced participation in sport were mentioned as problems by 17% of schools. Most schools said that children with asthma were encouraged to take part in sports as normally as their condition allowed.

Discussion

The number of children known to have asthma by the schools in this survey varied from 0 to 12%. The mean figures of 3·6% in primary and 2·9% in secondary schoolchildren are similar to the number of children diagnosed as having asthma in previous community surveys[2 5] but almost certainly underestimate the prevalence of recurrent wheeze that would respond to treatment for asthma.[3] In Nottingham there is no systematic method by which schools are informed if a child has asthma. Most schools depend on parents to volunteer this information, but we do not know how reliable this system is. A substantial number of children were not allowed to keep their inhalers with them during school hours and had either to request them or rely on their teachers to supply them when necessary. Children may feel inhibited in having to approach a teacher for their medication, and as teachers had received no training in this area and were unsure when treatment should be given it is unlikely that inhalers were being used optimally.

This survey has identified certain questions about the management of asthma in schools that need more detailed investigation. Firstly, how well are schools informed about pupils with asthma? Should a more formal means of communication be established between family practitioners and the school health service, so that the latter can ensure that teachers are made aware of medical problems? Secondly, how much access should children have to their inhalers? There are strong arguments for allowing children to keep bronchodilators required for symptomatic relief, although teachers may need more reassurance about their safety If prophylactic inhalers are needed in school they could be more justifiably handed over to the teachers. Thirdly, should teachers be given instruction in the management of childhood illnesses, either in teacher training or later in their career, so they feel better equipped to supervise children with common health problems? The school medical service is available for advice but perhaps could play a larger role in educating teachers and in the supervision of children with asthma.

We are grateful to Dr E More and Dr E J Hiller for their support and interest in this study

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Serological evidence of herpes simplex virus infection in atopic eczema

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SUMMARY Twenty three of 113 patients (20%) with atopic eczema had neutralising antibodies to herpes simplex virus compared with 34 of 113 matched controls (30%), an insignificant difference. This suggests that children with atopic eczema are no more likely to acquire herpes simplex infection than normal children.

While patients with atopic eczema are notoriously susceptible to severe skin infections with the herpes simplex virus,[1] it is not clear whether they are more prone to herpes simplex infection than children of the same age without atopic eczema. We therefore looked for serological evidence of herpes simplex infection in a group of children with atopic eczema and compared the seropositivity rate at different ages with control children of the same age and sex admitted to hospital .

Patients and methods

Patients with atopic eczema from the north west of England who attended the department of child health at our hospital were studied. Blood was routinely taken at the first visit from those most severely affected to exclude immune deficiency and to estimate the serum IgE concentration. Serum samples from 121 consecutive patients (81 boys and 40 girls) collected between January 1982 and July 1984 were available for study. No special enquiries were made about a previous history suggestive of herpes simplex infection, but a further five patients from whom blood was taken specifically because of herpes simplex infection were excluded.

These patients with atopic eczema were matched against children of the same age and sex from the catchment area of the North Manchester Regional Virus Laboratory, who were referred to hospital during the study period and from whom blood was taken to exclude virus infection. The request cards accompanying the blood specimens were examined, and if eczema, herpes simplex, or malignant disease were mentioned the specimen was excluded.

Complement dependent serum neutralising antibodies to herpes simplex virus type 1 (strain VR_3) were detected by a modification of the microneutralisation test of Pauls and Dowdle.[2] Heat inactivated serum samples were tested in quadruplicate at dilutions of 1:5 and 1:10. Any serum that contained neutralising antibodies at a dilution of 1:5 was regarded as seropositive.

Results

The results are summarised in the Table. When findings in children aged 6 months or less were excluded (as their antibodies were probably maternal in origin) 23 of the 113 patients (20%) had antibodies to herpes simplex virus compared with 34 of the 113 controls (30%). The difference between the two groups was insignificant ($\chi^2=2{\cdot}34$, $p=0{\cdot}12$) Patients over the age of 6 months showed a progressive increase in the incidence of antibodies to the virus with age, whereas the increasing incidence with age was less consistent in the control group.

Table *Neutralising herpes simplex virus antibodies in children with atopic eczema and control children*

Age	*Patients*				*Controls*			
	Boys	*Girls*	*Total*	*(%)*	*Boys*	*Girls*	*Total*	*(%)*
<7 months	0/4	3/4	3/8	(37)	4/4	1/4	5/8	(62)
7–23 months	1/25	0/10	1/35	(3)	4/25	4/10	8/35	(23)
2–4 years	7/30	3/16	10/46	(22)	6/30	10/16	16/46	(35)
5–14 years	10/22	2/10	12/32	(37)	5/22	5/10	10/32	(31)
Total*	18/77	5/36	23/113	(20)	15/77	19/36	34/113	(30)

*Not including subjects under 7 months (see text)

Discussion

As in any hospital based study the patients in this report were selected because their eczema was either unusually severe or particularly refractory to treatment. Such patients are possibly more susceptible to herpes simplex infection than children with milder eczema. The control group was also imperfect in that the controls were not drawn from exactly the same geographical area as the patients, they were not matched for social class, and some of them possibly had eczema

The results showed that there was no significant difference between the overall herpes simplex seropositivity rates of the two groups, which were similar to those reported for Edinburgh children in 1967.[3] Our findings suggest that children with atopic eczema are no more likely to acquire herpes simplex infection than normal children. The severity of initial herpes simplex infections in some children with atopic eczema, combined with troublesome recurrent herpes infections in others, may give rise to a false clinical impression of a greater incidence of infection. Our results do not indicate what proportion of initial herpes simplex infections were subclinical, skin infection, or gingivostomatatis. We have been unable to produce serological evidence to confirm the claim that children with atopic eczema are more often infected with the virus than normal children,[4] and the general claim that these children are more susceptible to viral infections[5] requires further substantiation.

We thank Professor Garcia de Lomas, who did much of the laboratory work during a sabbatical visit to the Regional Virus Laboratory, and Professors M Longson and S Shuster for their helpful comments

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Carbon monoxide concentrations in infant deaths

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SUMMARY Carboxyhaemoglobin measured in 50 infant deaths showed no significant difference between home and hospital deaths nor between explained and unexplained deaths. Carbon monoxide toxicity is unlikely to have an important role in the pathogenesis of sudden infant deaths. The generally low carboxyhaemoglobin concentrations are probably due to endogenous production.

Carbon monoxide poisoning as a factor in the pathogenesis of sudden infant death has been questioned.[1] Previous studies have been limited to North America,[2 3] and carboxyhaemoglobin values for infant deaths in the United Kingdom seem to be unavailable.

Patients and methods

A consecutive series of 50 infants who died in South Yorkshire aged 1 week to 2 years was studied between January and November 1985. There were 12 hospital deaths with ascertainable cause (group A), 11 explained deaths at home (group B), and 27 unexplained deaths at home (group C). The boy to girl ratios in groups A, B, and C were 4.8, 4.7, and 17·10, respectively In group A the duration of admission to hospital varied from one day to one year.

Carboxyhaemoglobin was measured using the spectrophotometric technique of Katsumata *et al*[4] This method does not give a positive bias when analysing samples containing a high proportion of fetal haemoglobin. Values for 16 summer home deaths and 22 winter home deaths were compared to evaluate the possible effect of differences in seasonal domestic ventilation. The Mann-Whitney U test was the statistical method used.

Results

No association was found between carboxyhaemoglobin concentrations and postmortem interval nor between carboxyhaemoglobin concentrations and age. Mean carboxyhaemoglobin concentrations for groups A, B, and C were 2·9% (range <0·5–6·7%), 2·2% (range <0·5–4%), and 1·9% (range <0·5–4·7%), respectively. The difference in carboxyhaemoglobin values between explained deaths (groups A and B) and unexplained deaths (group C) was not significant. No significant difference was found in values between boys and girls (between all groups) nor for values obtained for summer and winter home deaths.

Discussion

The lack of significant difference in carboxyhaemoglobin values between the explained and unexplained deaths and between home and hospital deaths argues against carbon monoxide poisoning being a significant factor in the pathogenesis of sudden infant deaths.

Carbon monoxide is normally generated endogenously in the body from haemoglobin degradation;[5] while its precise physiology is still unclear, diffusion through the lungs is a recognised mechanism of elimination. Consequently pneumonia or other disease that interferes with pulmonary gas exchange may result in raised carboxyhaemoglobin concentrations. This may explain two relatively high values recorded for infants dying in hospital; one infant had cytomegalovirus pneumonia and the other had alveolar immaturity associated with prematurity.

Among infant deaths at home in Michigan (USA) carbon monoxide toxicity was found not to be a significant factor.[2] On the other hand, carboxyhaemoglobin concentrations in excess of 5% were found in six of 141 infants aged less than 2 years in Chicago (USA).[3] Two had considerably raised values (34 and 49%) and were thought to have died from associated asphyxia. The values were much lower in the other four, and of these three had pneumonia.

Faulty combustion in domestic heating and cooking appliances is a potential source of exogenous carbon monoxide. If the carboxyhaemoglobin concentrations among the home deaths were the result of such emission lower values among infants dying in summer, when home ventilation would be likely to be more efficient, would be expected compared with winter concentrations. This was not found, suggesting that the carboxyhaemoglobin present was mainly derived from endogenously generated carbon monoxide.

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Group B streptococcal infection presenting as sudden death in infancy

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SUMMARY Two infants aged 3 and 8 months were found dead in their cots. Postmortem cultures yielded group B streptococci from multiple internal sites, and cytomegalovirus was also isolated from the lungs of one. These cases show the value of microbiological culture in the investigation of sudden infant death.

Serious infection with group B streptococci may occur at any age but has been seen most commonly in neonates [1 2] An early onset disease with respiratory distress and septicaemia or meningitis may develop within the first week of life as a result of acquisition of the organism from the mother at birth; this occurs particularly in babies of low birth weight and when there is prolonged or complicated labour or premature rupture of the membranes. Obstetric factors are thought to act by increasing the dose of the organism or the time the baby is in contact with it or by exposing the baby to the organism at an unusually early stage of development.[3] Another component of the problem may be that young babies lack the protective effect of a commensal flora on the body surfaces. Later onset disease in neonates often features meningitis and is thought to be due mainly to cross infection from staff or other babies in the nursery

Beyond the neonatal period serious group B streptococcal infection becomes much less common.[2] In a review of reports to the Public Health Laboratory Service systemic infection in neonates outnumbered that in older infants by 10 to one.[3] The sources and predisposing factors of infection in this later age group are largely unknown. We report two rapidly fatal infections in infants, one with a concurrent cytomegalovirus infection.

Case reports

Case 1. A 3 month old breast fed boy, who was developing normally, visited Yorkshire with his parents in December 1985. On the day after their arrival he was restless and sniffling, as though he had a congested nose. He was put to bed at 1300h that day and found dead at 1630h.

Necropsy was performed on the second day after death. There was oedema and vascular congestion of both lungs and some congestion of the liver. The thymus and spleen were enlarged with weights of 40 and 35 g, respectively (normal reference weights 10 and 16 g). There was no macroscopic evidence of meningitis. Histological examination of the lung revealed an interstitial pneumonitis, but no intracellular inclusions were found in this or other tissues examined.

Postmortem specimens yielded a pure growth of tetracycline resistant group B streptococci from lung, spleen, and cerebrospinal fluid (CSF). Typing of the organisms, at the Division of Hospital Infection, Colindale, showed that they were all type Ia/c and susceptible to phages in the Colindale group B streptococcal typing set. Culture of specimens in the department of virology, Leeds Public Health Laboratory, yielded cytomegalovirus from lung but not from nose, throat, or CSF.

Case 2. A healthy 8 month old girl, still partly breast fed, lived with her parents and one sibling in North Yorkshire One day in December 1985 she developed a slightly hoarse voice and was noticed to be more 'clinging' than usual. The next day she was put to bed in seemingly normal health at 2030h but was found dead the next morning.

Necropsy performed on the day after death showed petechial haemorrhages in the thymus and pericardium and oedematous, congested lungs weighing 180 g (normal reference weight 109 g). The spleen was congested and the thymus weighed 30 g (normal reference weight 8 g). Histology showed a focal interstitial pneumonitis, but no intracellular inclusions could be found

Postmortem specimens yielded tetracycline resistant group B streptococci from the nose, both main bronchi, lung, blood, and spleen but not from CSF. Typing in the Colindale laboratory showed that all isolates were type Ia and resistant to bacteriophages. CSF culture yielded no viruses.

Discussion

The heavy growth of group B streptococci from multiple systemic sites in these infants is good evidence of the cause of infection and death.

Meningitis is often seen as a feature of group B streptococcal infection at this age, and in one of our patients the organism was isolated from the CSF. The finding of cytomegalovirus in the lungs of the first patient could be simply coincidental, but it raises the possibility that acute viral disease might underlie and potentiate group B streptococcal infection in some patients.

An impressive aspect of these infections was the rapid course to death, giving no time to establish a diagnosis or begin treatment. A similar rapidly fatal course was noted in 50% of infants who died in a recent survey of group B streptococcal disease in Britain,[4] including one baby who, like ours, was found dead in his cot. A few years ago one of us reported a young adult with systemic group B streptococcal infection who, in similar style, was unexpectedly found dead in his bed.[5]

The presentation and initial necropsy findings suggested a diagnosis of the sudden infant death syndrome, which has been defined as "the sudden unexpected death of an infant in which a thorough postmortem examination fails to reveal an adequate cause of death";[6] without microbiological culture the diagnosis of acute streptococcal septicaemia would have been missed.

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Personal practice

Management of urinary tract infection

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The urinary tract is a common site for bacterial infection in childhood. Population screening for bacteriuria has revealed a slight male preponderance in the neonatal period, but thereafter it is more prevalent in girls, becoming as much as 50 times more common by the age of 5 years. Follow up of asymptomatic bacteriuria in schoolgirls has failed to show any convincing evidence that its discovery by screening can materially alter the outcome.[1] In preschool children the difficulties encountered in obtaining uncontaminated urine samples, together with the low acceptance rate, militate against cost effectiveness[2] Moreover, most renal scars observed are already present at initial investigation,[3] and their prevalence in infants is, disappointingly, as high as it is in older children.[4]

The practising paediatrician should therefore be concerned mainly with the management of *symptomatic* urinary tract infection (UTI), and the two basic aims of treatment are the relief of symptoms and the prevention, or at least limitation, of damage to the renal parenchyma. Experimental work in refluxing piglets has shown that the scarring process can be initiated within one week of introducing pathogenic bacteria into the bladder,[5] and there is good reason to believe that this may apply to children. Treatment with antibiotics of first infections in young children should therefore be regarded as a matter of urgency The wide range of suitable antibiotics now available has made treatment a comparatively simple matter Management, however, is more than just eradicating infection, it is also concerned with diagnostic reliability, alleviation of associated symptoms not directly due to bacteriuria, assessment of underlying structural abnormalities and the potential risk of future upper tract damage, and careful follow up of selected at risk patients throughout the growth period.

Clinical diagnosis

Despite the availability of simple and reliable techniques, the diagnosis of UTI in practice remains haphazard I am still referred patients who have been given antibiotics without having had a urine culture taken beforehand and often without adequate physical examination. It should be remembered that, at initial investigation, one third of girls are found to have vesicoureteric reflux and one fifth associated renal scarring (reflux nephropathy),[3] so that imaging of the urinary tract is mandatory in proven cases. How far unconfirmed cases should be subjected to invasive diagnostic procedures often presents a dilemma

Careful history taking and physical examination are fundamental. The dysuria caused by genital inflammation, especially common in prepubertal girls, and that caused by UTI are indistinguishable. Urge incontinence is often accompanied by vulvitis and constipation, and the latter may cause quite severe, intermittent abdominal pain, especially in the left flank where it is liable to be misinterpreted as having a renal origin. Abdominal examination should therefore take note not only of whether the kidneys and bladder are palpable but also of whether the descending colon is distended. Rectal examination is rarely called for, but failure to inspect the genitalia is inexcusable as vulvitis is many times more common than UTI and is often responsible for a raised urinary leucocyte count Examination should also include measurement of the blood pressure and neurological screening for evidence of sacral nerve root defects

Bacterial diagnosis

Confirmation of the diagnosis of UTI requires demonstration of the presence of pathogenic bacteria in the bladder urine by cultural techniques Infecting species are mostly enterobacteria—for example, *Escherichia coli, Klebsiella* species, and faecal streptococci. Proteus infection sometimes complicates obstructive uropathy, but this organism often colonises the male genitalia, when it may cause diagnostic difficulty. Staphylococci rarely cause UTI in children. Unfortunately, there are no simple 'dipstick' tests that are completely reliable; those based on bacterial consumption of the already minimal urinary glucose concentrations, or on conversion of urinary nitrate to nitrite, can be taken as good evidence of UTI when they yield positive results but unfortunately have unacceptably high false negative rates.[6] The most widely used cultural method is the viable colony count, which relies on the fact that bacteria incubated in the bladder urine at body temperature will have multiplied many times in two to three hours, whereas contaminant bacteria washed off the genitalia during voiding will not. A significant colony count is $>10^5$/ml; borderline counts of 10^4–10^5/ml can be regarded as unimportant if there is a mixed growth but may require repetition if associated with a single pathogen. The reliability of this method depends, firstly, on the urine specimen having been obtained by 'clean catch' or midstream technique and, secondly, on the midstream sample being plated out within one hour of voiding. Provided that the genitalia are clean, antiseptic swabbing is unnecessary.[6]

Information obtained from mothers often reveals that the specimen has been carefully collected at home at 0730h, reaches the doctor's surgery by 0900h, and is later despatched to the local hospital laboratory, so that a delay of some three hours is not uncommon. Contaminant bacteria will continue to proliferate at room temperature to yield borderline or even 'significant' counts and, as they are enterobacteria themselves, distinction from true bacteriuria may be impossible. If a delay between micturition and culture is unavoidable metabolism of contaminants can be inhibited by either refrigeration at 0–4°C or the addition of sodium borate to the specimen. The problem can also be overcome simply by inoculating a dipslide, by either immersion or 'dipstream' technique.[5] Colony counting has fortunately obviated the need for catheterisation in children old enough to void urine on request, but there remains a problem in very young children. The application of a Hollister U-bag, in which the voided urine seeps through pores into a separate space that isolates it from contact with the perineum, is an acceptable initial procedure in that a negative result reliably excludes UTI. As a result of the the high false positive rate, however, bag specimens that yield raised bacterial counts must be repeated and, if doubt remains, a suprapubic aspiration may be required.

The paediatrician with a special interest in renal disorders will find a simple microscope and Fuchs-Rosenthal leucocyte counting chamber of great help in the outpatient clinic. With the minimum of training, bacteria and cells can be identified and the latter counted. Routine Hema-Combistix testing and microscopy has been the practice in my renal clinic for more than 20 years and has the twofold advantage that the accompanying parent can be warned of a possible UTI or reassured as appropriate and that only those samples that show suspicious abnormalities (about 10% of the total) need be submitted to the microbiology laboratory for the more costly procedure of culture and sensitivity testing. In a prospective survey we failed to identify either bacteria or leucocytes in only 6% of infected specimens, whereas 15% of uninfected samples gave leucocyte counts $>10/\text{mm}^3$,[7] indicating that pyuria is less reliable evidence of UTI, contrary to popular belief.

Investigation

It is still widely taught that girls do not need to be investigated unless UTI is recurrent. This is an unwise policy, particularly in preschool children, who are vulnerable to upper tract damage if vesicoureteric reflux is present. Imaging of the urinary tract should be carried out after treatment of the first documented infection, preferably after an interval of two weeks, to allow acute inflammation to subside

The conventional method of visualising the upper urinary tract is intravenous urography (IVU). This entails both venepuncture and radiation, and in older children it is being progressively replaced by ultrasonography as radiologists gain experience with this non-invasive technique It is prudent to combine this procedure with a plain abdominal radiograph to exclude radio-opaque calculi and facilitate review of the lumbosacral spine At present we still perform IVU in proven UTI in children less than 3 years old, but in older children, and in younger ones where doubt exists about the diagnosis of UTI, we have found ultrasonography to be a reliable screening procedure. When abnormalities are revealed IVU is performed subsequently. In a comparison of simultaneous ultrasonography and IVU in 100 children with UTI it was recently reported that ultrasonography missed 12 out of 37 abnormalities detected by IVU.[8] As these consisted mostly of minor urinary tract dilatation and there was only one instance of failure to detect serious scarring, however, these results may be regarded as encouraging.

Conventional, fluoroscopic voiding cystourethrography is the only fully reliable means of diagnosing vesicoureteric reflux. Fluctuations in the excretion curve of ^{99m}technetium labelled diethylene triaminopenta-acetic acid may suggest reflux but the discrimination from intermittent partial obstruction is poor, and the anatomical detail needed to plan treatment cannot be obtained by this method. The instillation of a radionuclide into the bladder may yield semiquantitative information and minimises the radiation hazard but does not eliminate the need for catheterisation, which, in inexperienced hands, can prove so traumatic to a small child. We have solved this latter difficulty by having the catheterisation performed by our urodynamics nurses, whose success is attributable not only to their technical skill and experience but also to their patience and sympathy in first explaining the procedure to parents and children. We therefore continue to perform cystourethrography routinely in children under 5 years old, even in the light of a normal IVU, which can sometimes be obtained despite the presence of appreciable reflux, and in older children if renal scarring is seen on the IVU. It is not a good practice, however, to perform cystourethrography without first having reviewed the IVU or ultrasound films as an occasional child with UTI will show, for example, pelviureteric obstruction, and cystourethrography would become a needless investigation.

While radiological investigation of the urinary tract may seem straightforward, in practice a number of difficulties are encountered and attention to detail is essential. For some 15 years it has been the practice at this hospital to hold weekly meetings of nephrologists, surgeons, and radiologists, at which current radiographs, ultrasound scans, and radionuclide scans are reviewed. This is an important occasion that improves communication, to the benefit of the patients, and facilitates discussion of techniques. It is widely used by district hospital paediatricians as a means of obtaining expert radiological opinion, and from our observations it is clear that techniques vary considerably A common fault is inadequate bowel preparation before IVU, leaving the renal outlines concealed by gas and faecal shadows. As most children with UTI have unrecognised constipation pretreatment with laxatives is essential. Deficient cystourethrographic technique is also common; failure to take post-micturition films and to include the renal areas make it impossible to assess the severity of reflux

Treatment with antibiotics

While there is now a bewildering array of urinary antimicrobials available, most are needed only for dealing with the problem of bacterial resistance, which is fortunately rare in childhood, and the list of antibiotics for regular use is best confined to a few, well tried drugs. Most initial infections are caused by bacteria that are sensitive to trimethoprim, and in young children, in whom it is generally advisable to begin treatment without awaiting the result of laboratory sensitivity tests, this is the drug of choice It need be given only twice daily. Even first infections are often at least partially resistant to sulphonamides, nowadays, and co-trimoxazole has no advantage over plain trimethoprim.

Nitrofurantoin is equally effective but may cause nausea and vomiting, especially in young children who can only take the liquid preparation. Although four doses a day are recommended, in practice two are adequate Nalidixic acid can also be used, but parents should be warned of the possible occurrence of severe headaches and vomiting due to a hypersensitivity reaction causing benign intracranial hypertension [9] Amoxycillin and cephalexin are also suitable for short term use, but bacterial resistance readily develops, and these drugs are unsuitable for prophylaxis.

The recommended duration of treatment has varied from six months to a single dose. Controlled comparisons of treatment for six months versus two weeks[10] and one week versus a single dose[11] have shown the shorter courses to be equally effective Longer treatments merely postpone the next relapse and are unnecessary except where prophylaxis is indicated. The pharmacokinetics of trimethoprim indicate that this drug is suitable for single dose treatment,[12] which has obvious advantages in terms of both cost and compliance and is therefore an appropriate way to treat infrequent, recurrent UTI in children with radiologically normal tracts. In children aged less than 5 years, in whom the risk of reflux nephropathy is higher, it is wise to follow the treatment of first infections with a single nightly half dose of the same antibiotic until investigation has been undertaken

Low dosage chemoprophylaxis is indicated in children with appreciable reflux, in children awaiting surgical relief of urinary obstruction, and in selected patients with neuropathic bladder who experience repeated symptomatic UTI or in whom there is considered to be a risk of upper tract damage. Asymptomatic bacteriuria in the child with a radiologically normal urinary tract requires no treatment as there is a high spontaneous remission rate, and treatment may be followed by symptomatic relapse.[1] Prophylaxis plays a useful role, however, in those puzzling prepubertal girls who experience repeated, symptomatic infections despite a normal urinary tract and lose much school time. It may have to be continued until the menarche, and parents require sympathetic explanation and reassurance that such prolonged treatment is not harmful. The two most used drugs are trimethoprim and nitrofurantoin, both given in a single nightly dose of 1–2 mg/kg/day. Older children can take the slow release, encapsulated nitrofurantoin preparation, 'Macrodantin', which eliminates nausea.

Symptomatic management

A liberal fluid intake should be encouraged because the ensuing polyuria exerts a bladder washout effect, which helps to reduce bacterial colonisation. Children with symptomatic UTI generally experience involuntary frequency, but those without this symptom should be discouraged from 'holding on' (as they often do when voiding causes dysuria) as this will lessen the washout effect.

The treatment with antibiotics of bacteriuria typically gives prompt relief from dysuria, but urge incontinence, with or without nocturnal enuresis, often persists. In a urodynamic study of 37 girls with reflux we found that these symptoms correlated strongly with the finding of detrusor instability, which was present in as many as 28 patients.[13] Urge syndrome seems to be an associated condition rather than the cause of UTI. Some important relations between urge syndrome, constipation, and UTI have emerged from years of clinical observation[14] and have recently been confirmed by means of combined urodynamic studies and rectal manometry.[15] The Figure attempts to explain these relations, from which it is evident that successful management of urge incontinence might favourably influence the treatment of UTI.

Disappointingly, treatment with anticholinergic drugs has, in our experience, been associated with a high incidence of both therapeutic failure and side effects.[14] The key to the problem is defective perineal muscular relaxation, the result of 'holding on' in an attempt to prevent wetting. Simultaneous contraction of the urethral and anal sphincters is unavoidable because of their common nerve supply. The increased sphincter activity promotes faecal retention, and treatment of constipation is an essential component of management. I do not favour the aggressive regimen of daily enemas that has been advocated[15] but recommend the adoption of a high fibre diet and, if necessary, prescribe Senokot initially. Unfortunately, the suggestion of wholewheat foods often meets with resistance, and success ultimately depends on patiently persuading the whole family to participate in dietary changes for their own benefit.

As uninhibited detrusor systole prompts voluntary closure of the external urethral sphincter the intravesical pressure generated is often higher than that associated with voiding.[13] Cystometry shows that, as the bladder fills, these isometric pressures increase until, sooner or later, they exceed the maximum urethral pressure, at which point mechanical leakage occurs. The child must therefore be trained to void urine sufficiently often to prevent this happening, usually at intervals of not more than two hours. Defective perineal muscular relaxation often defeats this aim, and it is the passage of soft, bulky motions without straining or discomfort, afforded by the high fibre diet, that facilitates such relaxation.

Successful treatment of urge incontinence is desirable as this condition serves to encourage both vulvitis and ammoniacal dermatitis of the labia, and these in turn may aggravate sphincter spasm through increased sensory input and promote bacterial colonisation. Severe, symptomatic vulvitis usually responds to two to three weeks' application of 0·01% dienoestrol cream, which stratifies the epithelium and may yield a lasting effect. Asymptomatic vulvitis is almost normal in prepubertal girls, however, and requires no treatment; in the absence of diabetes mellitus or immune deficiency it is never caused by vaginal candidiasis, and antifungal creams, so commonly prescribed, are useless. A small but none the less important detail is that many schools, state or private, supply toilet paper that is abrasive, and girls with perineal soreness will not use it; the remedy is to take soft tissue from home. Naturally, girls should be taught to wipe the anus backwards and bathe daily, but there is no evidence that more rigorous perineal hygiene helps, except where there is the problem of faecal incontinence resulting from severe constipation or more rarely from sacral neuropathy.

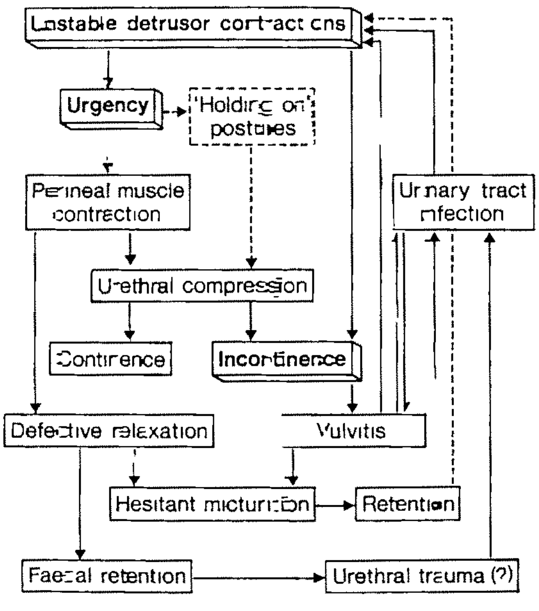

Figure *Hypothetical interrelations between urge syndrome, constipation, and urinary tract infection*

Underlying defects

Where imaging reveals an obstruction or the presence of calculi in the urinary tract surgical relief should be sought without delay to minimise permanent renal parenchymal damage, and chemoprophylaxis should be maintained until this has been achieved The management of neuropathic bladder has been transformed by the introduction of intermittent self catheterisation as an alternative to urinary diversion. Our comparatively recent experience suggests that, provided the patient is initially instructed in correct catheter technique and regularly monitored by skilled and sympathetic nursing staff and that faecal incontinence can be minimised by dietary management with or without laxatives, bacteriuria can be satisfactorily controlled by means of chemoprophylaxis. Indeed, in the absence of reflux or upper tract dilatation it is worth a trial without regular antibiotics, and it is questionable whether asymptomatic bacteriuria in such patients needs treatment

Vesicoureteric reflux

The relation between vesicoureteric reflux and renal parenchymal scarring is firmly established and the term reflux nephropathy is preferred to chronic pyelonephritis.[16 17] We previously reported that 98% of scarred kidneys were drained by refluxing ureters and that the incidence of scarring increased with the severity of reflux [16] The scarring produced experimentally in pigs with reflux and sterile urine is not comparable with human reflux nephropathy in that it entailed obstruction, through progressive occlusion of the urethra.[18] There is little evidence, if any, that childhood reflux nephropathy occurs in the absence of UTI at some time In our series 47% of kidneys drained by refluxing ureters were not scarred,[16] and it now seems clear that intrarenal reflux must also be present if scarring is to develop. This is caused by the fusion of neighbouring papillae during embryogenesis to form compound structures in which some of the collecting ducts emerge in a concavity rather than tangentially to the surface [20] The development of typical, coarse renal scarring in the absence of reflux is, in our experience, quite rare [16] Whether P fimbriated *E. coli,* which adhere to uroepithelium through recognition of receptors related to the human P blood group, are capable of inducing pyelonephritic scarring by ascending the non-refluxing ureter, is still controversial.[21] An equally reasonable assumption is that the scarring had been caused by past reflux that had resolved spontaneously.

The essential aim of treatment of reflux is to protect the renal parenchyma from infection and the subsequent development of scarring As it is not possible to diagnose intrarenal reflux reliably during life those children at risk of reflux nephropathy cannot be accurately predicted, and it must be assumed that all children with vesicoureteric reflux have the potential for scarring. The few reports of radiologically diagnosed intrarenal reflux, however, have all been in children aged under 5 years;[19] moreover, the incidence of new scar formation declines steeply after the age of 7.[16 22 23] Therapeutic endeavours are therefore more likely to be effective when concentrated on younger children

There are two treatment options· the surgical correction of reflux and the maintenance of uninfected urine. Although improved renal growth after ureteric reimplantation has been claimed, prolonged follow up of patients treated medically indicates a continuing trend towards resolution of reflux.[17] The Birmingham reflux study group recently reported the results of a prospective, controlled trial of operative versus non-operative treatment of severe vesicoureteric reflux, which showed no significant differences in renal function, renal growth, the development of new scars and progression of existing ones, and the incidence of breakthrough UTI, after an observation period of two years.[4] This is a short duration of follow up for a chronic condition; the results after five years' observation,[22] however, confirm the earlier findings, and it is concluded that neither form of management has any particular advantage Further studies are continuing, but in the meantime the choice of treatment remains an individual one; the inconvenience of admission to hospital and a permanent abdominal scar, the relative risks of a surgical procedure compared with prolonged chemotherapy, and the likelihood of compliance with the latter all need to be considered in reaching a decision.

If chemoprophylaxis is the option chosen, how long should it continue? An interesting finding of our study was that the development of new scars and the progression of existing ones occurred only during the first two years' observation and not between two and five years. Moreover, these developments bore no relation to the occurrence or absence of breakthrough UTI during the first two years,[4 22] so that an over obsessional attitude to chemoprophylaxis can no longer be justified My current practice is to continue chemoprophylaxis for not more than two years in older children, and in younger children until they are 7 years old, when the risk of further renal damage becomes minimal.

Ongoing care

Most children with UTI in whom the urinary tract is structurally and functionally normal can return to general practitioner care, but a minority will suffer from repeated infections and may benefit from continued paediatric supervision. These are mostly prepubertal girls; resolution usually occurs around the time of the menarche, although some girls later experience recurrence with the advent of sexual activity and may need guidance. A small number of patients will reach adulthood with persistent reflux but normal kidneys. Preliminary information suggests that they are not at greater future health risk than those without reflux; the degree of reduction of renal function is related to the presence of renal scarring rather than the reflux itself.[24] These patients may therefore be discharged with reassurance during adolescence

Children with reflux nephropathy should, ideally, be followed up in a paediatric clinic until physical and renal growth have ceased, when a final radiological and functional assessment should be performed. When scarring is unilateral a healthy contralateral kidney will undergo structural and functional hypertrophy so that there is no measurable reduction of total glomerular filtration rate.[14] The development of persistent proteinuria in the presence of scarring, however, is usually indicative of secondary glomerular sclerosis, possibly owing to hyperfusion of surviving, undamaged nephrons, and should be carefully monitored. A potential risk is hypertension and, on discharge from paediatric care, the patient without proteinuria should be advised to obtain an annual blood pressure check from the general practitioner. Patients with either proteinuria or extensive bilateral reflux nephropathy are under threat of impaired renal function, and possibly end stage renal failure, and should be referred to an adult nephrologist for ongoing care

Compliance is a potential impediment to successful long term care, and it is essential to develop rapport with the patients and their families. Confidence is more likely to develop if consultations are unhurried and sympathetic. As children grow older they should be addressed directly rather than through their parents, and older teenagers should be encouraged to attend the clinic unaccompanied, so that personal health matters can be discussed privately. Most girls will appreciate a few words of counsel regarding the pill and pregnancy. Oral contraceptives are associated with an increased risk of hypertension, and young women with reflux nephropathy should be advised to undergo regular blood pressure checks; they would very likely ignore advice to avoid the pill There is an increased risk of bacteriuria during pregnancy, and patients should be cautioned to mention their previous health problems at the antenatal clinic to ensure vigilance.

Conclusion

Experience during the past 20 years, and the careful collection of data by research workers, has led to considerable rationalisation of the management of UTI It must be acknowledged that our inability to diagnose reflux, and particularly intrarenal reflux, and in many cases to begin treatment before renal scarring develops is a major handicap Nevertheless, correct management may at least diminish some of the misery associated with symptomatic UTI and limit the progression of renal damage.

The importance of accurate diagnosis and prompt treatment in children less than 5 years old cannot be overemphasised

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Current topic

Violence and children

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The media, in its everyday portrayal of the lot of children suggests that they are often subjected to more and prolonged violence, which is of a greater refinement of cruelty than ever before The aggression meted to children is a good barometer of the amount in society, and judging by today's events that amount is high. Physical, emotional, and sexual batterings all seem to be escalating. Even the natural events in the world seem to be more violent, with earthquakes, volcanic eruptions, droughts, and starvation abounding. In many ways the world has always been so, but what is new is the ease with which we become acquainted with the problems as soon as they occur. They are seen with a reality that was unthinkable a quarter of a century ago. The scale of violence is now such that many people are very worried by it.

For over a decade a few people have repeatedly said that violence begets violence and that the GIGO (garbage in garbage out) of the computer world is the VIVO (violence in violence out) of the human world The crimes of today seem to be more bizarre than before and affect not only the very young but also the very old In the eyes of some of the legal and medical profession there is a clear association between the evil as seen on videos and read in books and the subsequent actions of certain beholders. Not everybody is affected by seeing the extremely violent videos; at the most it would seem to be a minority of the viewers, but the size of the problem is unknown Society has always had the violent and the perverted within it; what viewing violence seems to do is to provoke and release these tendencies. It lowers the resistance of some who under normal circumstances are able to contain their deep, violent feelings; they then live out what they have seen. The warnings have been given but have passed unheeded until recently.

Factors in the increase in crime rates

The crime rate in the United States of America doubled in the decade after 1958, and in the quarter of a century after 1951 violence against the person increased by a factor of 10. Two thirds of the burglars in our prisons are under the age of 21—scarcely out of the paediatricians' age group. All the indicators of crime show an increase, which for homicide, rape, robbery, and assault is exponential.[1] There are obviously many factors that affect the behaviours of a society, religion is one, the media is another. Over the last 25 years there has been a decrease in the practice of the former and an increase in the usage of the latter. The American child is said to see 11 000 murders on television before the age of 14 and 7·5 violent episodes per viewing hour.[2] The British child, by contrast, sees only four violent episodes per viewing hour, and those between the ages of 6 and 11 view for 25 hours each week. An average American adult reads a book for a total of five hours each year.

Video 'nasties'

About two years ago videos with a much higher order of violence began to be imported into the United Kingdom. They became available to all ages Usually the violence is intimately interwoven with deviant sexual actions and the whole portrayed with such vivid reality as to make the viewer feel part of the scene. Children's nursery rhymes and fairy tale stories down the ages have contained an element of violence, but it is wrapped up in a fantasy that is quite apart from the real child's world and, albeit frightening, can usually be rationalised by the child as pure fantasy The fairy tale 'baddies' always met their fate due, and good triumphed. In today's video 'nasty' evil triumphs, and of good there is none.

It was the quantum jump in the order of violence and evil that made some parliamentarians establish a parliamentary group inquiry. The report of this group has been published[3] but the work started long before parliament placed on the Statute Book the Video Recordings Act, which made it lawful to classify all video tapes, as a first step to protecting families against offensive videos. Paediatricians helped with the questionnaires for the inquiry. I had misgivings initially about the paediatricians' experiences; I thought it most unlikely that more than a few would know anything about these violent videos, despite the fact that the evidence was that a large proportion of their patients were viewing them. The misgivings proved to be ill founded. The survey of paediatricians was concerned only with experiences and opinions There had to be a start, and this seemed as good a way as any. The 'scientific' way of testing the effect of video nasties on children would be to expose one group to them and perform an observational comparison with controls who had not seen them. No ethical committee nor paediatrician would sanction this. We are in the business of alleviating suffering not administering it

Paediatricians' responses to the questionnaire on video nasties

Many members of the British Paediatric Association (BPA) were circularised with the questionnaire designed by Lord Swinfen and myself to assess their experience and opinions on the video nasties. We endeavoured to avoid troubling members who were not involved with clinical practice with children or who were concerned with those too young to view the videos. There was a 38% response rate, which compares favourably with the 32% response to the BPA's own request for information about its 1985 Annual Meeting. (Personal communication.) It was surprising that 56% of those who responded had been aware of violent videos being an important factor in children's and adolescents' lives before the survey. Almost a third of the respondents usually or occasionally inquired about whether their patients viewed violent videos. About one in six (14%) of the respondents had been given accounts of at least one patient whose emotional state or behaviour had been influenced by watching violent videos. About 40% of those respondents who inquired about patients' viewing patterns found, however, that the videos had influenced the children's emotional or behavioural state.^{3}

No less than 70% of the paediatricians who responded were of the opinion that the viewing of video nasties was likely never to be helpful, but 4% thought that it could be sometimes helpful. No respondent thought that the video nasties could be often or always helpful. Ninety per cent of the respondents thought that video nasties were likely to be sometimes harmful, but 17% believed that they were always harmful. Less than 1% of the respondents thought that the video nasties were likely to be never harmful.

One half of those respondents who inquired about their patients' viewing patterns and had experience of violent videos being influential on their patients' symptoms thought that the experience of viewing these violent videos was either occasionally or usually harmful. One respondent thought that viewing violent videos was either occasionally or usually beneficial. The acute symptoms associated with video nasties included nightmares, sleeplessness, and nocturnal enuresis. Two children were noted to regress to a younger behaviour pattern and depression. Fearfulness and anxiety about being left alone were especially common Sometimes the children seemed to be absolutely terrified. The acute behaviour disorders followed so closely after the viewing of video nasties that they are highly likely to be related.

The long term effects will be difficult to assess because of the intervention of so many other factors in the child's life and the child's personality that makes him want to view this sort of material. One paediatrician commented 'that for most children there are inbuilt defence mechanisms which allow compensation for the input of horror and pornography. However, I think that there are some susceptible children and adults who do not have this facility and who will be permanently damaged'. Intelligence may be a factor that aids the adjustment to the viewing of the violent videos, less intelligent children may not have the same ability to prevent copying the type of abnormal behaviour they see on a film. One doctor had encountered a 19 year old boy who, directly after watching a video at a friend's home, went home and repeated the incident he had seen on the film by raping his 13 year old stepsister. The boy admitted that he had been influenced by the video film he had seen He had a low intelligence and came from a deprived family background.

The family milieu

Children receive their moral values and attitudes from their family from the early days. Today, many children are brought up in violent homes, amid unimaginable terrors, and often they become desensitised to violence and grow up with the belief that it is the norm These children may well regard violence as seen in the media and videos as the normal standard of behaviour. Children who are blessed with a peaceful upbringing are at risk of being acutely disturbed by the horror of the video nasties; this group are more likely to receive help from an understanding family and to have the harm mitigated. On the other hand, when children see the violent break up of families with murder on the videos and televisions at a time when they are experiencing the realities of family break up in their own home the damage from the media can drive them to breaking point. One doctor wrote: 'I am convinced in my mind that watching ordinary violent films on television increases the tendency to violence, depending on home background and the stability and security of the home, together with the parents attitudes' Another wrote: 'It is the chaotic families, about which we already have grave concern, who are heavy users of videos of all types; such families are unlikely to protect their young children from viewing unsuitable material'. The families who watch violent videos are probably themselves already violent and feed themselves thereon. One doctor wrote: 'Basic common sense would make one guess that the more violence is seen, the more it may be adopted as part of behaviour'. Another wrote. 'Our lives and attitudes are influenced by our experiences and it seems obvious to me that bad experiences will not be beneficial. The viewing of violence, etc., on television, particularly as it is shown in entertainment and not as an example of something to be avoided evil, inevitably, have a bad effect on children'.

One of the frightening effects of watching violence on video is that of causing imitative behaviour One paediatrician encountered children who were playing with drills and pretending to kill one another after watching a video entitled 'Driller killer One young man, aged 15, who was described as a loner' with reasoning problems, who 'fantasised about violence', read a lot of horror books, and regularly and often watched violent horrific video films, was convicted of murder having repeatedly stabbed an 8 year old boy to death.

Population survey

A survey of 4500 children between the ages of 7 and 16 of both sexes discovered that 45% of the children had seen one or more of the violent, horrific video films.[3] One third of all children aged 8 had already seen a video nasty by the age of 10 and half had seen at least one '18' rated adult film The favourite '18' rated films were concerned with the occult, horror, or pornography. One of the worrying features is that for many children their first introduction to sexual activity is through the scenes of explicit violence, rape, and sexual deviance. As with many undesirable activities boys are more often participants than girls and, furthermore, so are those in urban rather than rural areas. Parents who were described as lenient were more likely to have children who saw the videos than parents who adopted a more active protective role. Ninety per cent of the parents in the sample stated that society has a duty to help them to protect their children from seeing uncensored video films. One of the very interesting findings was that many parents were quite unaware that their children were seeing video nasties or '18' rated films. This arises because the films are seen in neighbours' homes often as part of an effort to entertain the children The host parents are apparently unaware of the nature of the films, as most of the material is bland enough and the horrific scenes are of brief duration. One of the undesirable assets of video cassette recordings is that the same piece of film can be replayed often. Some children expressed their appreciation of the fact that they could watch the 'interesting' part of the film several times without having to suffer the rest of the film

Conclusion

Western society is beginning to appreciate the dangers of propagating the image of violence. The pendulum has begun its return. The awfulness of many crimes against people of all ages, and the demonstration of violence on the streets, is making many people think it is time that children were given a more wholesome milieu within which to grow up. As paediatricians we pay great attention to optimal physical growth and the dietary conditions that determine this. Emotional health also depends on receiving good emotional 'food'. We prevent children from receiving poison by mouth; should we not speak up more against allowing them to receive poison by eye and ear. Many years ago St Paul was far more positive when he wrote: 'Finally brethren whatsoever things are true . . honest . . just . . . pure . lovely . . of good report, if there be any virtue, and if there be any praise think on these things.'[4]

It is a pleasure to acknowledge the debt owed to Lord Swinfen, the members of the parliamentary group enquiry scientific committee, and the many paediatricians who returned their completed questionnaires.

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Archives of Disease in Childhood, 1987, **62,** 431–433

Correspondence

Medical evidence in child abuse cases

Sir,

The letter by Hall *et al* would be an interesting response to a claim that speech delay in the absence of any other evidence of child abuse is a sufficient reason for action in the courts[1] Our paper says nothing of the kind[2] We were at pains to associate speech delay with other evidence of abuse, and it is implicit in our comments that inferring a link between speech delay and abuse requires evidence that the child has been in a depriving, neglectful, and understimulating environment. The problem with which we were trying to grapple is that for the medical witness such evidence is often secondhand and therefore may be regarded as hearsay, hence the need for inference It is the role of the social worker to tell the court what home circumstances are like If there is no evidence of adverse home circumstances and/or additional signs of abuse, such as failure to thrive or non-accidental injury, the case could not be taken to court in the first place nor would any sensible court make an order To quote from our article.

> 'Thus, while it is not possible, for example, to say that a child with speech delay must be neglected, if the speech delay is associated with physical injury or unexplained growth failure, it is reasonable to conclude that it is "likely" that home circumstances are responsible for both deficiencies.'[2]

This conclusion is given added weight by our experience that abused children with retarded speech almost always show spectacular improvement in foster homes. We have not seen a child show regression of speech development while fostered. It is exciting to see previously virtually non-speaking children blossom with adequate stimulation and care.

We see no reason to modify our view that delay in speech, a term which we believe to be plain English, in no way imprecise, encompassing retardation of language, understanding, and expression, is a common finding in children who have been abused. We refer all our cases for assessment to speech therapists, whom we believe are aware of all the undoubted pitfalls in deciding that speech deficiencies are probably due to lack of stimulation or deprivation We have found that in a group of 239 abused children over 1 year of age 48 (20%) were found to have sufficiently retarded speech to warrant active intervention As a further large number of children were not tested for various reasons the true percentage of problems is even higher, perhaps as high as 30%. We are also finding that a large proportion are running into major learning and behaviour difficulties. This hardly conjures up a picture of 'robustness' of speech development in the face of deprivation and abuse.

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Home monitoring in SIDS siblings

Sir,

I was interested to read the letter from Dr Swift and the reply from Dr Emery *et al* on apnoea monitoring and cot death.[1]

I have experience of home monitoring of over 300 siblings of victims of sudden infant death syndrome (SIDS) during the past eight years in both Ontario, Canada, and the Grampian region of Scotland. Two of these siblings died while being monitored.[2] As others have had similar experiences there is no doubt that these infants can die despite home monitoring equipment. There is no evidence yet available, however, for it to be stated categorically that such equipment does not save lives As implied by Emery *et al,* incomplete retrospective surveys, such as the Californian study they quote, are prone to bias and thereby unacceptable as evidence. The only way to answer the question is by a properly controlled randomised study such as that presently being undertaken by Emery *et al.*[3] Fortunately SIDS in a SIDS sibling is relatively rare, and it is therefore likely to take a further 15–20 years to complete this study at the present enrolment rate I hope by that time there will be a deeper understanding of the causes of the sudden infant death syndrome.

Perhaps this is looking at home monitoring from the wrong angle Ninety nine per cent of subsequent SIDS siblings will survive Most parents of these children, however, are extremely anxious and may often wake their newborn infant or even keep vigil Not only is such supervision extremely demanding and difficult for the parents to maintain, but the myoclonic jerks, irregular respiratory patterns, and other normal sleep related phenomena are disturbing to such parents Under these circumstances I would agree with Dr Swift that home monitoring is a relatively cheap and reliable method of allaying parental anxiety Even if this is purely a placebo effect, does it matter? If this is the case, however, then it would seem reasonable to choose a placebo that might just save the infant's life rather than one that is unlikely to do so

Most paediatricians in the United Kingdom use the Graseby Dynamics MR10 monitor and there is no reason to suppose that this equipment is in any way dangerous to the child. False alarms are relatively rare and occur mostly during the first few weeks of monitoring. Frequent weighing also has 'false alarms' every time the infant fails to gain weight. In my experience there are rarely difficulties with the weaning of parents off monitoring equipment

In Ontario home monitoring was stopped at an average age of just under 3 months[2]

Judging by the dozens of letters I have received over the years, most parents found home monitoring very effective in relieving their anxiety, despite having been warned that babies have died while on such equipment. Further evidence for this is that well over 90% of parents who have had one infant on home monitoring equipment request monitoring for their subsequent children.

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The school entry medical examination

Sir,

Whitmore and Bax put forward a cogent argument for retaining and improving the school entry medical examination[1] They point out that a fairly high proportion of children do not receive satisfactory health surveillance during their preschool years and emphasise the importance of the child receiving health care in relation to his functioning in school

It is disappointing that such a comprehensive assessment does not attempt to identify children with asthma, a condition that causes a great deal of avoidable disability in schoolchildren. Recent community based studies have shown that roughly one in nine primary schoolchildren will have had recurrent episodes of wheezing by the age of 8 and that many of these children will not have been diagnosed as having asthma[2] Failure to make the diagnosis of asthma is often associated with frequent absences from school, poor educational performance,[3] and inappropriate or inadequate treatment. This state of affairs is particularly unfortunate with a condition that is so easily diagnosed and where effective treatment is so readily available

There is no evidence that the management of childhood asthma is improving Indeed, admissions to hospital continue to increase and the number of deaths from asthma in children and young adults has almost doubled over the past decade[4] It is apparent that unless the diagnosis is made treatment will not be given. School doctors and school nurses are in a unique position and could easily identify most children with asthma by including the simple question 'Has your child ever wheezed?'[2] in their interviews or questionnaires. While this would not solve the problems of underdiagnosis and undertreatment, it would at least be a useful first step.

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Drs Bax and Whitmore comment.

We are grateful for Dr Couriel's comments. We did not include in our account the details of our parent questionnaire/interview, in which we do of course make enquiries about the child's history of respiratory illness. Apart from examining the child we have been reviewing, since the publication of the papers Dr Couriel refers to, the management of asthma in all children we see in school. We did emphasise in the paper that discussion on the management of illnesses, including asthma, is very much a part of the school doctors' and nurses' task

Improvements in child resistant containers

Sir,

In 1985 you published our paper that suggested that the voluntary agreement between the government and the pharmaceutical profession on child resistant containers had not resulted in a significant fall in accidental child poisoning in South Glamorgan.[1] Since that time we have been approached about whether we had evidence whether blister (or unit) packs were as effective as child resistant containers in preventing accidental child poisoning. It has occurred to us that it is possible to use data within our paper to answer this

We have compared the type of packaging used in the cases of accidental child poisoning in children under 5 years with solid dose prescribable medications (excluding aspirin and paracetamol) admitted to hospital in South Glamorgan for the years 1983, 1984, and 1985 with the type of packaging of similar medications in general use in South Glamorgan estimated by those handed into our pharmacy by patients admitted to our hospital in 1985 We have added 1985 figures for poisoning admissions to those contained originally in our paper (Table).

Table *Comparison of types of packaging used in cases admitted to hospital because of poisoning in 1983–85 and in the general population in 1985*

Type of packaging	*Group in whom packaging used*	
	Cases admitted to hospital due to poisoning	*General population*
Child resistant container	11	256
Blister or unit packs	26	78
Ordinary container	77	469
Unknown	8	0

These data confirm (using χ^2 analysis) that child resistant containers are effective in preventing accidental child poisoning ($p<0{\cdot}01$) but also suggest that they are much more effective ($p<0{\cdot}01$) than blister (or unit) packs We are assuming that the pattern of medicines handed into our pharmacy is similar to that in general use and therefore these figures should be taken with some caution, nevertheless, the scale of the differences we have shown suggests that blister or unit packaging should not replace child resistant containers as a method of preventing child poisoning.

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Should mothers with cystic fibrosis breast feed?

Sir,

Controversy continues about the wisdom of mothers with cystic fibrosis breast feeding their babies Studies on the sodium content of breast milk in patients with cystic fibrosis are conflicting.[1] [2] Nine patients with cystic fibrosis attending the Brompton Hospital have had successful pregnancies; samples of breast milk from two and colostrum from a third mother were studied

Case 1 delivered a healthy boy, weighing 2960 g, normally at term She breast fed and the baby gained weight along the 20th centile; weaning began at 3 months. Case 2 delivered a boy weighing 1640 g at 29 weeks' gestation, he required resuscitation and was brain damaged. He gained weight well, being weaned at 3 months Sweat tests in both infants yielded normal results Colostrum was collected from a third patient before lactation was suppressed because of maternal undernutrition.

Milk samples were obtained before feeding by drip collection into clean deionised containers and stored at −20°C Sodium and potassium concentrations were measured by flame photometry, chloride concentrations by conductivity, calcium concentrations by a colorimetric method, osmolality by vapour pressure osometry, zinc and copper concentrations by atomic absorption spectrophotometry, fat by hydrochloric acid catalysed transmethylation followed by gas-liquid chromatography, and immunoglobulins by radial immunodiffusion

The electrolytes and osmolalities (Table) were broadly within the normal range, the trace metals and fat tended towards the lower end. The immunoglobulin concentrations in case 1 at 28 weeks (with normal means in brackets[3]) were IgA 0·34 (0·365), IgG 0·7 (0·018), and IgM <0·05 (0·021) g/l. Colostrum from case 3 showed IgA 7·3 (1·26), IgG 1 3 (0·067), and IgM <0·05 (0·147) g/l

There was no evidence of raised sodium concentrations, in contrast with earlier observations, and our results are consistent with a recent report [1] The other constituents were also within normal ranges Our data do not suggest any absolute contraindication to breast feeding on the grounds of milk content, but maternal nutrition requires careful monitoring

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Table *Results of breast milk analyses in the three cases*

	Sodium (mmol/l)	*Potassium (mmol/l)*	*Chloride (mmol/l)*	*Calcium (mmol/l)*	*Osmolality (mOsm/kg)*	*Zinc (μmol/l)*	*Copper (μmol/l)*	*Fat (g/l)*
Case 1								
At 4 weeks	12	14 8	11	15	290			58 7
At 16 weeks								
Before feeding	4	12 1	9	10	295			40 6
After feeding	3	13	9	10 3	293			29 8
At 28 weeks	2	16 1	11	9 5	273	7 6	2 8	36 6
Case 2								
At 6 weeks	4	>8	7					
At 7 weeks	3	>10	6					
Reference values*	7 4 (2–20)	13 0 (9–17)	10 7 (2–21)	8 5 (4–16)	300±2 9	18 1 (2–47)	4 7 (1–11)	45 (13–83)
Case 3								
At 3 days (colostrum)	10	14 2			332			
Reference values*	21 7 (11–60)	18 9 (16–23)						

*Given as mean (range) except osmolality (mean (SEM))

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Book reviews

AIDS: Modern Concepts and Therapeutic Challenges. Edited by S Broder Pp 369: $83·50 hardback. Marcel Dekker, 1987.

Papers and books on the acquired immune deficiency syndrome (AIDS) are proliferating at a rate comparable with that at which the disease is spreading This authoritative book contains two introductory chapters, originating from the departments of Gallo and Montagnier, who first described the virus that causes AIDS The duplication continues with two chapters on molecular biology, epidemiology, and Kaposi's sarcoma. The remainder of the chapters cover important areas such as the variety of clinical manifestations, pathology, psychosocial aspects, and treatment. There is a short but detailed chapter on paediatric AIDS.

Paediatricians in the United Kingdom have had little experience of patients with AIDS, and our involvement has so far been confined to fielding awkward questions from parents of babies on the neonatal unit and from students and junior staff This complacent state of affairs is likely to change. The varied and non-specific presentation of paediatric AIDS causes problems in deciding which children to investigate. Where it is considered inappropriate to look for antibodies to human immunodeficiency virus (HIV) it is useful to have other 'markers' of infection. The chapter on paediatric AIDS by Parks and Scott offers guidance on these and many other relevant topics.

The rapidity with which knowledge and understanding of AIDS is expanding presents difficulties to book publishers. This book contains references from early 1986, yet already the name of the virus has changed from HTLV-3 to HIV, and EBV has been elucidated as the probable cause of the interstitial pneumonitis so characteristic of childhood AIDS. I recommend that paediatricians who wish to learn more about a fascinating disease and the virus that causes it should refer to this book I suspect it is too detailed for most general paediatricians to warrant the outlay of a personal copy.

F M POPE

Two-Dimensional Echocardiography in Infants and Children. By J P Lintermans Pp 299: £75·75 (US$ 114·00) hardback. Martinus Nijhoff, 1986

The scope of this book, as the title suggests, is strictly limited to cross-sectional echocardiographic imaging, which is only one aspect of modern cardiac ultrasound The text is intermittently in note form, in places the English is imperfect, and some of the nomenclature is outdated. The first chapter deals with 'left to right shunts' rather than with recognition of normal cardiac anatomy Sequential analysis, on which modern echocardiographic assessment of congenital heart disease is based (and made both more understandable and digestible) is dealt with briefly and relegated to the last chapter. This illogical approach results in both text and illustrations being unnecessarily repetitive The illustrations are on the whole of high quality and the chapters are adequately referenced, but overall this book cannot compete in either content or price with other currently available texts.

JOHN L GIBBS

Emerging Perspectives on Assessment of Exceptional Children. (Special Services in the Schools Vol 2 Edited by R E Bennett and C A Maher Pp 193: $24·95 hardback The Haworth Press, 1986

This multi-author American book is a state of the art description of assessment of children with learning difficulties Assessment is an information gathering process to make decisions and plan interventions. The clear need to link assessment to treatment programmes and their evaluation and the limitations of the 'norm based' classical psychometric techniques in this field hav proved to be the stimuli for the types o assessment this book describes

This book is easily read but mos paediatricians will be happy to absorb th philosophy of approach rather than th detail. Precise definition of learning difficulties seems to be as elusive as that o 'special needs', and although the genera principles of assessment apply to any child most of the examples in this book are o children in 'normal' schools who hav reading problems. There are several references to current American dilemmas in th field of 'special' education, particularl legal action as the stimulus to assessme and intervention for the individual chil

If a child is referred with reading problems 'classical' psychometric tests have a place, as discussed in chapters by Reschl and Lidz They emphasise that examinin how the child functions depends on environmental aspects, which must also b looked at systematically—that is, th classroom, teacher style, peers, and family Spear and Sternberg discuss informatio processing as an assessment tool—fo example, the difficulty with phoneme an syllable counting in children with readin problems Such an approach must complement the normative assessment but doe directly suggest remediation A test-teach retest approach is described in a multi author chapter on learning potential assessment Two other chapters give reviews o the neuropsychological test batter approach (useful if used for asset rathe than deficit intervention) and personalit testing (interesting but currently periphera to most remediation planning) Ted Hasselberg describes the development of computer systems for diagnosis—is redundanc around the corner? The chapter by Cec Reynolds on the necessity for some mathematical understanding of the relation between achievement and intelligence quotient scores is a timely reminder of the nee to define what we actually mean by learning difficulty

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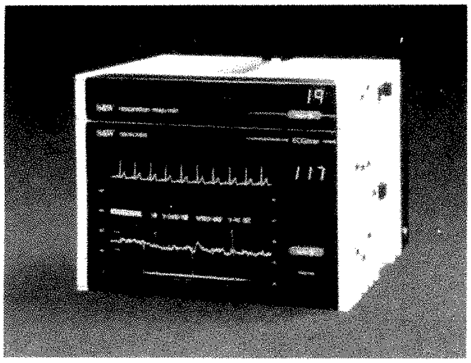

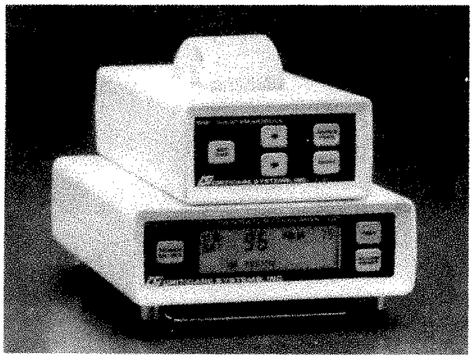

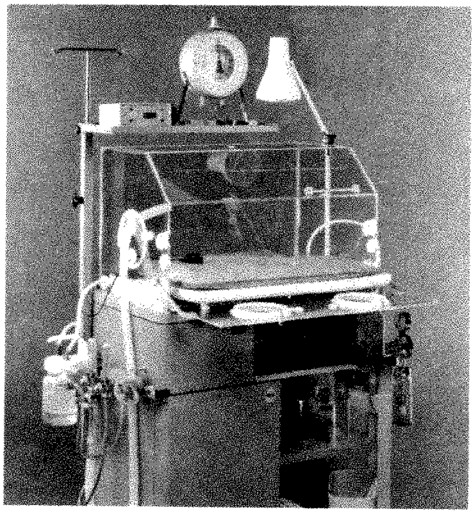

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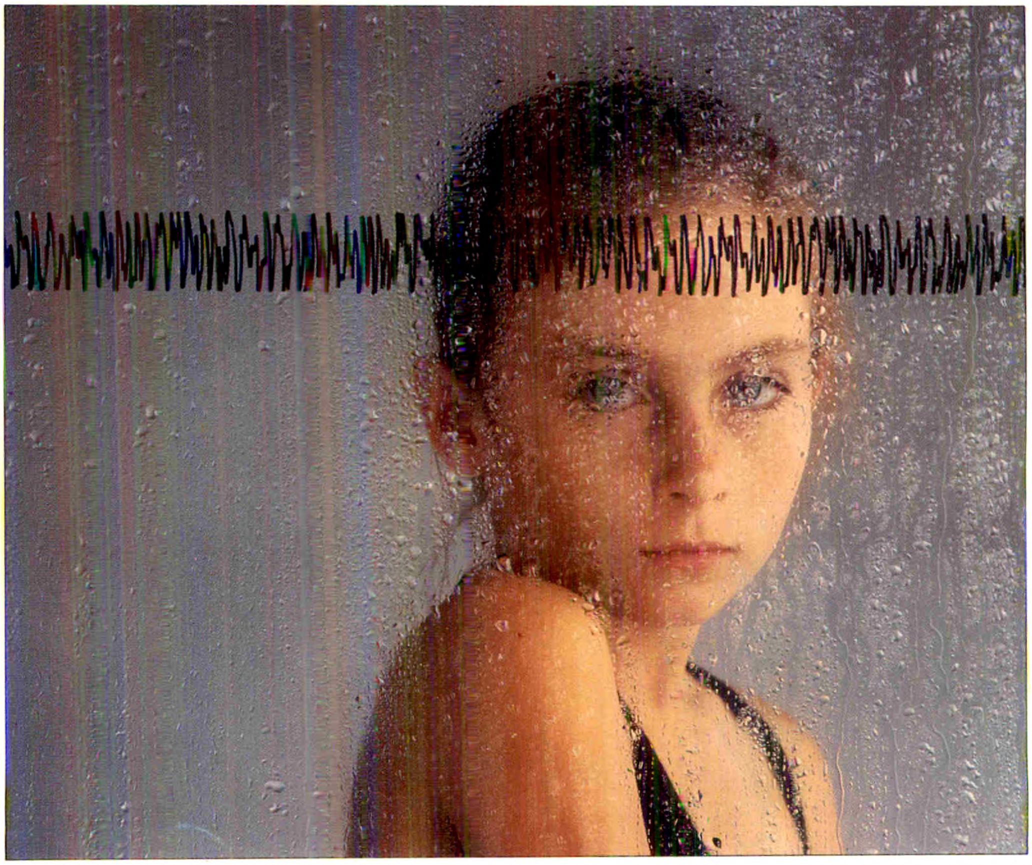

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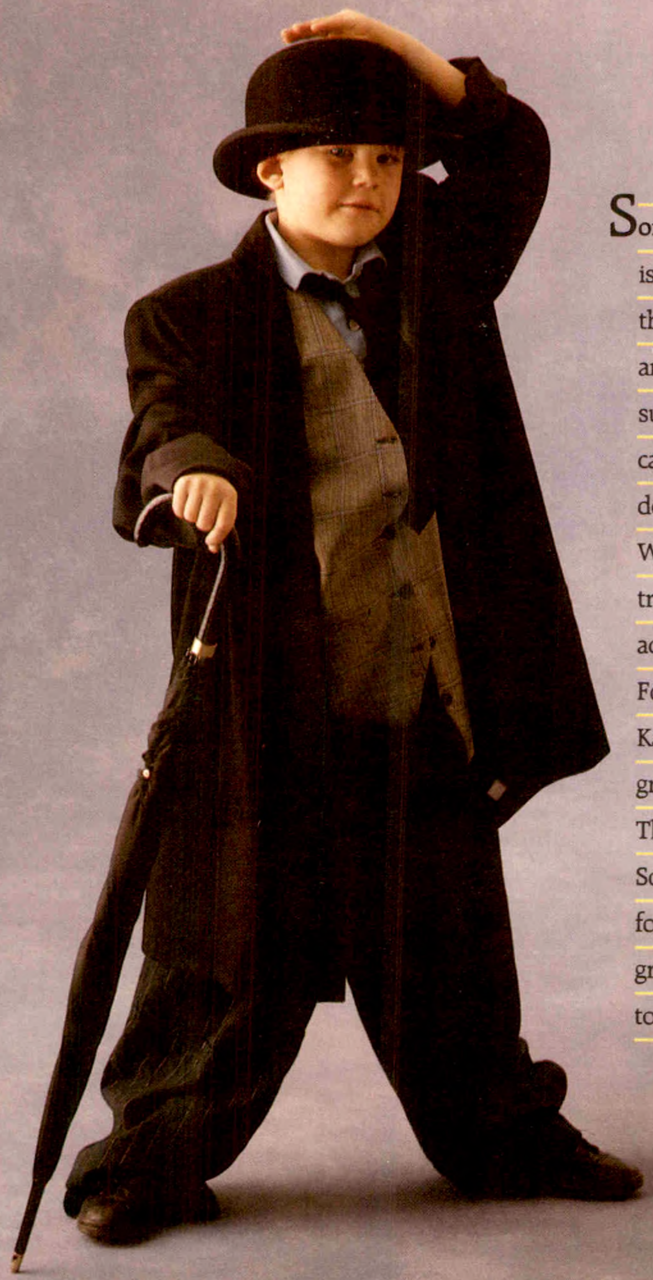

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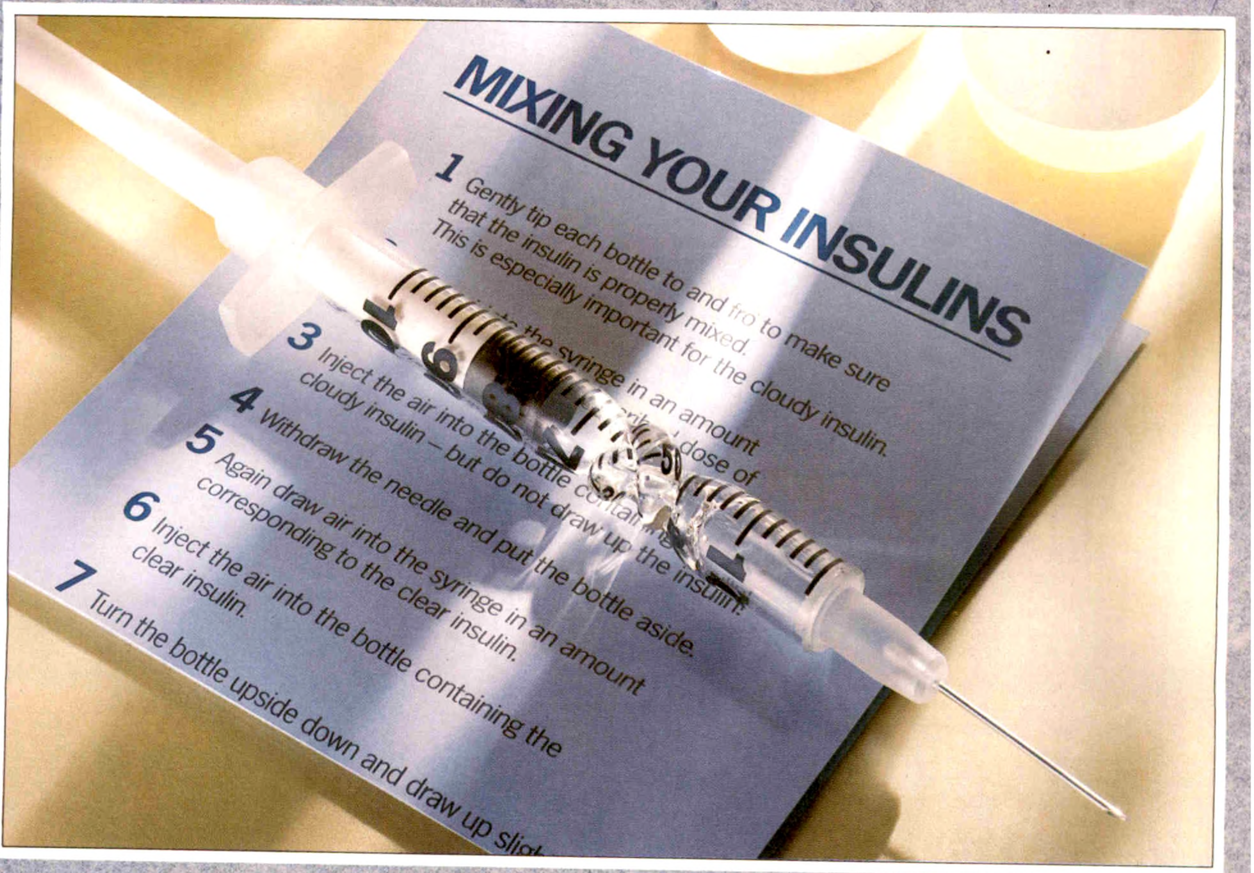

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Presentation 1. Epilim 200 Enteric Coated. A lilac-coloured, enteric coated tablet containing 200mg Sodium Valproate B.P. 2. Epilim 500 Enteric Coated. A lilac-coloured, enteric coated tablet containing 500mg Sodium Valproate B.P. 3. Epilim 100mg crushable tablets. A white, scored tablet containing 100mg Sodium Valproate B.P. 4. Epilim Syrup. A red, cherry-flavoured syrup containing 200mg Sodium Valproate B.P. per 5ml. 5. Epilim Liquid. A red, cherry-flavoured, sugar-free liquid containing 200mg Sodium Valproate B.P. per 5ml. **Indications** In the treatment of generalised, partial or other epilepsies. In women of child-bearing age Epilim should be used only in severe cases or in those resistant to other treatment. **Dosage and Administration** To be taken with or after food. Epilim may be given twice daily. Enteric coated tablets should be swallowed whole. **Monotherapy** *Adults:* Start at 600mg daily increasing by 200mg at 3 day intervals until control is achieved. (Maximum dose 2,500mg per day.) *Children over 20kg:* Initially 400mg/day with spaced increases until control is achieved. (Usually within the range 20-30mg/kg body weight per day.) *Children under 20kg:* 20mg/kg of body weight per day: in severe cases may be increased up to 40mg/kg/day. Increases above this only if plasma valproic acid levels, clinical chemistry and haematological parameters can be monitored. **Combined Therapy** It may be necessary to raise the dose when used with anticonvulsants which induce liver enzyme activity. Dosage of barbiturates should be reduced if sedation is observed. Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. **Contra-indications, Warnings** *Contra-indication:* Active liver disease. *Side effects:* Liver dysfunction including hepatic failure resulting in fatalities has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children under the age of three and those with congenital metabolic disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first 6 months of therapy and usually involved multiple anticonvulsant therapy. Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. The onset of an acute illness, especially within the first 6 months, which may include symptoms of vomiting, lethargy or weakness, drowsiness, anorexia, jaundice or loss of seizure control is an indication for immediate withdrawal of the drug. Evidence to date does not establish which investigation could predict this possible adverse effect; measurement of liver function should be performed in the first 6 months of therapy in those who seem most at risk and those with a prior history of liver disease. Hyperammonaemia without hepatic damage can occur, it is usually transient, but may occasionally present clinically. If so Epilim should be discontinued. Valproic acid inhibits platelet aggregation. Thrombocytopenia has been reported. Spontaneous bruising or bleeding is an indication for withdrawal of medication. Pancreatitis, tremor, weight gain, transient hair loss, increased alertness, aggressiveness, hyperactivity, amenorrhoea, stupor and oedema have been reported. **Drug Interactions** Epilim may potentiate monoamine oxidase inhibitors and other antidepressants. Loss of efficacy of oral contraceptive agents does not appear to be a problem. **Women of Childbearing Age** Valproic acid and sodium valproate, like certain other anticonvulsants, have been shown to be teratogenic in animals. In women of childbearing age the benefits of these compounds should be weighed against the possible hazard suggested by these findings and their pregnancies should be carefully monitored. **Product Licence Numbers** Epilim 200 Enteric Coated 0623/0006. Epilim 500 Enteric Coated 0623/0005. Epilim 100mg crushable tablets 0623/0015. Epilim Syrup 0623/0004. Epilim Liquid 0623/0016. **NHS Cost** Epilim 200 Enteric Coated 100 tablets £6.59. Epilim 500 Enteric Coated 100 tablets, £16.45. Epilim 100mg crushable tablets 100 tablets, £3.99. Epilim Syrup 200ml, £4.03. Epilim Liquid 200ml, £4.03. Further information is available from:

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Epilim
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Archives of Disease in Childhood, 1987, **62,** 435

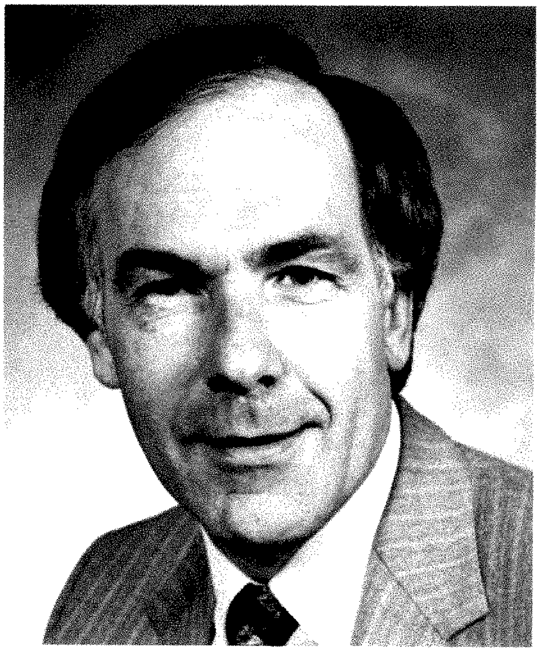
An editor departs

Roy Meadow joined Roger Robinson as coeditor of *The Archives of Disease in Childhood* in 1979. This month he retires from office having been senior editor for five years.

During the past nine years the number of original papers submitted has increased from about 450 to 850 each year and the total number of manuscripts to over 1000. The number of pages published has risen from about 1000 to 1300 each year. The publication time has fallen from 14 months to about four months due to a policy of accepting a ration of papers which would fill the space available. Another innovation was an increase in the number of commissioned articles. This has provided a background for the general reader and enabled the editors to accept sound, specialised, original work of limited appeal.

Before Roy Meadow became editor there were about nine annotations, two editorials, and four other similar articles a year; and now there are about 30 annotations, three editorials, and 24 personal practice or current topic papers. Some cosmetic surgery and a little colour added to the cover have provided the extra space needed for the larger number of titles. The Diamond Jubilee edition last year was his idea, and was published despite many obstacles. Instead of providing a conventional history of the Journal he devised new ways to interest writers in history and to capture the reader's eye.

While he was increasing the scope and quality of the Journal, other aspects of Roy's professional life expanded enormously. When he was appointed editor in 1979 he was a senior lecturer and the following year was appointed inaugural professor and head of the department of paediatrics and child health at St James's Hospital in Leeds. He had the task of developing a new university paediatric department during a period of financial stringency. He maintained his extensive research in nephrology, enuresis, and Munchausen by proxy, which is now known universally as Meadow's syndrome. His descriptions of this syndrome showed his ability to detect the vital fact within the mire of collected trivia and confirmed that bedside research was still alive.



His boundless enthusiasm for writing did not diminish, and the fifth edition of his popular undergraduate book *Notes on Paediatrics* was published in 1986. Two other books have been published since 1979, and a new book on paediatric kidney disease will be published this year. He has been editor of two editions of *Recent Advances in Paediatrics*, which has now become an essential part of every paediatrician's home library. Roy also generously provided nine chapters for editors of other books. He has been an examiner for the final MB in seven universities, chairman of the Association for Child Psychology and Psychiatry, and a member of his District Health Authority, a post which has caused more frustration than all the rest put together.

Despite all these pressures on his time he has always put the work of The Archives first. When he was phoned at home over the weekend or during the evening he was always available to give a coeditor wise advice at those moments when a problem seemed insoluble. He had the knack of choosing the perceptive referee who was able to improve the quality of the paper by constructive criticism.

We thank Roy for the nine years of hard labour he devoted to the Journal which flourished under his guidance, and we wish him many more years of productive writing.

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Annotations

Haemorrhagic disease and vitamin K

By 1950, haemorrhagic disease of the newborn (HDN) seemed fairly well understood. It caused spontaneous bleeding in the early days of life, typically in breast fed infants, and was associated with a clotting defect that rapidly corrected with vitamin K. It was established that cow's milk was a richer source of vitamin K than mother's milk and that small supplements of cow's milk given to breast fed infants conferred protection against HDN.[1] While the role of vitamin K prophylaxis was not universally accepted, many maternity units adopted a policy of giving it routinely to all neonates and reported a dramatic decline in the incidence of HDN.[2]

In the mid-1950s, however, came reports of increased severity of jaundice and raised incidence of kernicterus after the introduction of routine vitamin K prophylaxis, and confidence in the practice was shaken.[3] At that time the type of vitamin K commonly used was a water soluble, synthetic analogue, vitamin K (Synkavit) often in doses exceeding 50 mg even in premature infants. It was subsequently established that high doses of vitamin K_3 in neonates caused haemolysis, while vitamin K_1 (phytomenadione, fat soluble and occurring naturally in green vegetables) was safe and gave protection against HDN in doses as small as 0·5–1 mg given intramuscularly.[4] Nevertheless, the association of vitamin K with kernicterus had become firmly entrenched in people's minds, and in many maternity units (perhaps the majority in the United Kingdom) the practice of giving it routinely to all babies was either abandoned or never established. Instead, prophylaxis was usually reserved for babies considered especially at risk from HDN, and this selective method seemed a satisfactory compromise.[5]

Vitamin K research

Recent years have seen the development of sensitive assays for vitamin K in blood and milk, the discovery of PIVKAs ('Proteins Induced in Vitamin K Absence'—clotting factor precursors that require carboxylation to become functional), and further elucidation of the mechanisms of the vitamin's action.[6] [7] Information about liver storage is becoming available.[8] Nevertheless, our understanding of HDN remains far from complete. Among the questions awaiting answers are: What determines the extent of the baby's vitamin K stores at birth? How long do these stores last? Is malabsorption of vitamin K the major factor in causing HDN? Do gut flora make any contribution to the baby's vitamin K supply?

Vitamin K prophylaxis

While admitting the wide gaps in our knowledge of HDN, two facts are undisputed. Firstly, the condition is virtually confined to breast fed infants who are not given vitamin K prophylaxis. Secondly, it carries a high risk of morbidity or death. Now that it is again common for babies to be solely breast fed, even to the exclusion of supplementary formula feeds while breast feeding is becoming established (perhaps a significant source of vitamin K in the past), we strongly recommend that all infants should receive prophylaxis. The experience in our own unit, where six cases of HDN occurred in 17 months,[9] emphasises that a selective policy of vitamin K prophylaxis is no longer adequate.

Given that all infants should receive vitamin K, how should it be given? From the experience of the 1950s and '60s it is well established that vitamin K_1 (1 mg given intramuscularly) protects against HDN, and reports to the contrary are exceedingly rare. The injection, however, does cause some discomfort to the baby, is viewed with suspicion by many parents as an 'unnatural' intervention in the birth process, and has occasionally led to disaster when the baby was inadvertently given the Syntometrine intended for the mother.[10]

Vitamin K can also be given orally—indeed, this was the method of choice in one of the earliest studies.[11] Prophylaxis by this route is potentially less certain as the dose may not be swallowed, absorbed, or metabolised, particularly if the infant has underlying disease yet undiagnosed—for example, cystic fibrosis, biliary atresia, α_1 antitrypsin deficiency, or abetalipoproteinaemia. In one well documented case a baby seemed to have temporary malabsorption of vitamin K alone.[12]

An oral dose of 1 mg vitamin K_1 gives peak plasma concentrations some 300 times the normal adult concentrations (which in turn exceed cord blood concentrations by a factor of 10[13]) but only 5% of those achieved after intramuscular injection of the same dose.[14] If the intramuscular dose is not considered to be excessive it could be inferred that a larger dose should be used orally for equally effective prophylaxis It is by no means certain, however, that peak plasma concentrations after prophylaxis relate to either the total amount of vitamin absorbed or retained and there is good evidence that a 1 mg oral dose gives protection [15] If considered necessary an increased oral load of vitamin K_1 could be achieved in several ways, including a larger single dose at birth, repeated oral doses for breast fed infants, or supplementation of breast feeding mothers to increase the vitamin K content of their milk. The latter methods, requiring repeated doses to either baby or mother, have the attraction that effective prophylaxis may be more reliably extended into the second and third months of life, when there is still risk of late onset HDN and stores from a single prophylactic dose at birth may be exhausted. Compliance with a regimen of repeated doses, however, may be poor and difficult to supervise and our own preference is to give a single prophylactic dose at birth.

For reasons of acceptability to parents, safety, convenience, and cost we currently use a 1 mg oral dose of vitamin K_1 for routine prophylaxis and continue to use intramuscular prophylaxis in infants at special risk from HDN—that is, those born prematurely or admitted to the special care baby unit for any other reason and those born by traumatic delivery or to mothers taking oral anticonvulsants. We have now used this policy in some 25 000 babies and have not seen any further cases of HDN.

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Pseudomonas infections in cystic fibrosis

Pseudomonas aeruginosa is the main pathogen of the genus pseudomonas in cystic fibrosis, although *Pseudomonas cepacia* has been increasingly isolated from patients with cystic fibrosis in recent years. This article gives an overview of the microbiological factors that account for their pathogenicity. Colonisation, progression to chest infection, and management are also reviewed.

Microbiology of *Pseudomonas aeruginosa*

In the laboratory *P. aeruginosa* can grow in the presence of a wide variety of substrates and will even multiply in distilled water and weak disinfectants. This great adaptability is also reflected in its expression of certain virulence factors in response to environmental conditions. The use of classical genetic techniques (chemical mutagenesis, transduction, and conjugation) has helped in the characterisation of its virulence factors, and the recent introduction of recombinant deoxyribonucleic acid techniques should increase our understanding of pseudomonas infections, which range from acute septicaemia, as in patients with burns, to chronic infection in patients with cystic fibrosis.

The most striking difference between strains of *P aeruginosa* isolated from patients with cystic fibrosis and those isolated from patients with other conditions is the production of an exopolysaccharide β1,4-linked mannuronic acid and L-guluronic acid, usually referred to as alginate; this exopolysaccharide is readily recognised in the laboratory because the colonies have a mucoid appearance. In vitro, production of alginate is an unstable characteristic, but mucoid variants are selected in vivo. Alginate protects the organism from opsonisation and phagocytosis[1] and forms an elastic gel inside which microcolonies develop, in the presence of high calcium ion concentrations such as occur in the lungs of patients with cystic fibrosis. Alginate also contributes to virulence by enhancing colonisation by mucoid strains[2] and it has recently been proposed that alginate contributes to lung damage due to the formation of immune complexes.[3]

P. aeruginosa produces several extracellular virulence factors, the most toxic of which is exotoxin A. Exotoxin A is toxic for human macrophages, which may assist the survival of the organism and have been shown to contribute to chronic lung infection in rats. An inverse relation between anti-exotoxin A antibodies and clinical scores, in patients with cystic fibrosis, also suggests that exotoxin A contributes to infection.[4] A recent study showed that 100% of strains of *P aeruginosa* from patients with cystic fibrosis produce phospholipase C,[5] this acts preferentially against phosphatidylcholine, which is the major component of lung surfactant. *P. aeruginosa* also produces several proteases, including an elastase, which contribute to local tissue damage; recent studies have shown that these inhibit neutrophil chemotaxis and the C_3 and C_5a components of complement, and break down IgA.[6]

Colonisation by *P. aeruginosa* and progression to disease

Colonisation of the respiratory tract by *P aeruginosa* is encountered in 17–90% of patients attending cystic fibrosis clinics,[7] rates increase with age, the mean age of onset being 9–10 years.[8] Most patients initially experience intermittent colonisation with non-mucoid forms, which subsequently become mucoid and intractable; it should be noted that all strains genetically code for production of alginate, but a suppressor gene prevents expression of this characteristic in non-mucoid forms.

Initially, the patient may produce little or no sputum and organisms may be scanty, which makes detection of colonisation difficult. Brett *et al* have recently shown that patients with cystic fibrosis develop IgG antibodies, detectable by enzyme linked immunosorbent assay (ELISA), to *P aeruginosa* surface antigens shortly before or within one or two months after colonisation.[9] The persistent isolation of mucoid *P. aeruginosa* is associated with clinical deterioration,[10] and Brett *et al* have shown a correlation between the immunological changes and the severity of the infection.[11] Currently, most patients with cystic fibrosis who die with pulmonary complications are infected with mucoid forms of *P. aeruginosa.*

Treatment of *P. aeruginosa*

Antipseudomonal penicillins combined with an aminoglycoside antibiotic, in high dosage and together with physiotherapy, have been the mainstay of treatment in most centres. While this leads to improved well being and lung function, eradication of the organism is uncommon and transient. More recently, intravenous ceftazidime, or imipenem and cilastatin in combination, or oral quinolones (nalidixic acid derivatives) have been tried. Subsequently, the patient's clinical condition usually deteriorates again over a period of three to four months

Regular two week courses of antibiotics every three months have been shown to improve the five year survival,[8] but many centres relate the timing of courses to clinical state. In one study *P. aeruginosa* was eliminated by antibiotics from half the patients who were treated within six months of developing IgG antibodies to the organism,[9] as detected by ELISA. It remains to be seen if other workers will have similar experiences and whether this approach will have a major impact on long term survival. Long term treatment with nebulised antibiotic was shown by Hodson *et al*[12] and in a number of other studies to reduce the number of subsequent admissions to hospital and improve well being Resistance and allergy sometimes develop, however, and the selection of other organisms, especially *P. cepacia,* is another possibility.

Resistance to antipseudomonal penicillins and aminoglycosides is increasing and in one centre resistance rates to carbenicillin, piperacillin, and gentamicin have been reported to be 70%, 30%, and 40%, respectively. Despite their short clinical use, resistance to ceftazidime, imipenem/cilastatin, and the quinolones has also occurred.

Microbiology of *P. cepacia*

P. cepacia, although less closely related to *P aeruginosa* than many pseudomonads, shares its versatility for growth and survival Study of its virulence factors is only in its infancy Apart from the production of proteases and lipases by most isolates from patients with cystic fibrosis,[13] little else is clear.

P. cepacia infection

The number of centres that have reported this organism is increasing and one centre in the United States reported that 20% of their patients were colonised in 1983, with an annual rate of acquisition of 8%.[14] Overall, the scale of the problem is substantially less, many centres reporting few or no cases. Many patients who become colonised show no change in their natural history, but some show an accelerated clinical deterioration and a few experience a fulminant infection with severe necrotising pneumonia demonstrable at necropsy. In reviewing the published works, Goldman and Klinger[13] drew attention to the finding in one centre that 42% of patients with cystic fibrosis who died were colonised with *P. cepacia.* Treatment of the infections is difficult as the organism is inherently resistant to antipseudomonal penicillins, aminoglycosides, and colistin, but clinical improvement has been reported in some cases treated with ceftazidime.

Cross infection with the organism does occur and current therapeutic regimens for *P. aeruginosa* probably exert a selective pressure for this organism. While much of our attention is focused on *P. aeruginosa,* it is clearly important to study *P cepacia* in depth.

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Original articles

Hydrolysed wheat based oral rehydration solution for acute diarrhoea

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SUMMARY A randomised three cell study was carried out in 78 children with acute diarrhoea to evaluate the relative efficacy of oral rehydration solution (ORS) made from partially hydrolysed wheat grain, cooked rice powder, or glucose. Twenty six patients with comparable age, body weight, duration of diarrhoea, and degree of dehydration were studied in each of the three groups. Initial rehydration was carried out by using intravenous Dhaka solution within one to two hours followed by administration of oral rehydration solution. The mean ORS intake during the first and second 24 hours of treatment in patients with cholera receiving wheat-ORS and rice-ORS was significantly less compared with those receiving glucose-ORS. The stool output during the same period in patients receiving wheat-ORS and rice-ORS was significantly less compared with those receiving glucose-ORS. Similar trends in both ORS intake and stool output were observed during the next 24 hours.

The efficacy of oral rehydration treatment in replacing the loss of water and salts in stools in cases with watery diarrhoea has been well established.[1–4] It has almost eliminated the need for treatment with intravenous fluids, except in very severe cases. The discovery of glucose facilitated transport of sodium and water in the small intestine[5] led to the use of glucose-salt solution for effective rehydration of patients with acute watery diarrhoea. The absorption of glucose is, however, rate limiting, and increasing its concentration leads to osmotic diarrhoea. A number of possible ways of further enhancing the absorption of sodium (and water) in acute diarrhoea have been tried. Studies by Molla *et al*[6 7] and subsequently by Patra *et al*[8] have shown that rice powder was as effective as, or even superior to, glucose for the treatment of acute diarrhoea as far as both requirements of oral rehydration solution (ORS) and stool volume were concerned. Rice and other cereals are inexpensive and, being staple foods, are easily available and acceptable. In the intestine they yield glucose and amino acids slowly, reducing the risk of osmotic diarrhoea. To our knowledge, no study has been undertaken using hydrolysed wheat as a substitute for glucose in ORS, although wheat is a staple source of energy and proteins for a considerable proportion (about 43%) of the total world population.

Wheat extract prepared by enzymatic digestion[9] was obtained from the late Professor A Dahlqvist. The preparation is rich in protein (11·5%) and low in lactose and fat (0·5%) content, with linoleate as the main component. Lysine is the limiting amino acid. It also contains vitamins and minerals (including thiamin, niacin, iron, zinc, and calcium). In preliminary studies we have tested its acceptability and digestibility[10] and its use as an alternative source of nitrogen and energy during rehabilitation of malnourished children. (Alam AN, Khanum S, Khatun A, Molla A, Rahaman MM. Unpublished observations.) The present study was undertaken to evaluate the relative efficacy of this hydrolysed wheat based electrolyte solution compared with other available oral rehydration solutions in the management of dehydrating diarrhoea.

The composition of the wheat grain extract was verified in our biochemistry laboratory and consists of carbohydrates 87%; protein 11·5%, fat 0·5%; and ash 1·8%. The carbohydrates in the extract include glucose (dextrose) 3%, maltose 60%, maltotriose 15%, higher maltosaccharides 15%, and isomaltose, sucrose, and fructose (2% of total carbohydrate).

The wheat extract was obtained as a slightly coloured spray dried powder (about 2% water). The extract was completely soluble in water.

In vitro acid hydrolysis converts about 80% of the wheat extract into glucose so that if 50 g is added to a litre of ORS about 40 g of glucose can be expected to be released in the intestinal lumen. The osmolality of a 5% solution of the wheat extract as measured after adding electrolytes recommended by the World Health Organisation (WHO) was found to be 280 mmol, which is iso-osmolar with plasma.

Patients and methods

Seventy eight children aged 1–8 years who attended the treatment centre at our hospital from April 1983 to April 1984 were studied. They had a history of watery diarrhoea of less than 72 hours' duration with moderate to severe dehydration. Clinical examination was performed on admission. Patients with severe malnutrition (<60% weight for age of 50th centile of National Center for Health Statistics) or systemic illnesses, such as bronchopneumonia, otitis media, and meningitis, and those who had received antibiotics before admission were excluded. Written consent was obtained from the legal guardian of each child before the study. The children were randomised according to the permuted block design to ensure equal numbers of subjects in each treatment group.

Electrolyte content of the solutions was the same as that recommended by the WHO (Na^+ 90 mmol/l, K^+ 20 mmol/l, Cl^- 90 mmol/l, and HCO_3 30 mmol/l) in all three groups. One group received the electrolyte solution with 50 g/l wheat powder (wheat-ORS), the second group with 50 g/l rice powder (rice-ORS), and the third group with 20 g/l glucose (glucose-ORS) (Table 1). The wheat extract or rice powder and the electrolytes were packaged separately. The solutions were prepared by adding the electrolytes to the wheat powder dissolved in or the rice powder cooked in a litre of water. Normal hospital diet (rice and chicken) was allowed soon after initial rehydration. Nursing mothers were encouraged to continue breast feeding. The oral rehydration preparations and plain water were offered ad libitum. All patients were rehydrated initially by intravenous Dhaka solution (Na^+ 133 mmol/l, K^+ 13 mmol/l, Cl^- 88 mmol/l, and HCO_3 48 mmol/l) within one to two hours, in accordance with WHO guidelines,[11] and were offered the study solutions after initial rehydration.

Body weight was recorded on admission and every eight hours thereafter. Any vomitus was measured and recorded. No antibiotics were given during the study. On admission 3 ml blood were drawn for the estimation of electrolytes, packed cell volume, and specific gravity. This was repeated after 24 hours and before discharge. Eight hourly intake/output charts were maintained. Plastic uribags were used to collect urine separately. Microscopic examination and culture of stool samples were carried out on admission for *Vibrio cholerae, Salmonella* spp, *Shigella* spp, and enterotoxigenic *Escherichia coli.* Isolates of *E. coli* were tested for heat labile and heat stable enterotoxins.[11 12] Rotavirus was tested by an enzyme linked immunosorbent assay method.[13]

The rate of purging, change in body weight, serum specific gravity, urine output, sugar content of stool before and after hydrolysis were measured every 24 hours to compare the efficacy of the three kinds of oral treatment. Patients were discharged after passing the first formed stool.

Patients who required intravenous fluid after beginning treatment with oral fluid because of recurrence of signs of severe dehydration with decreased body weight up to or below the admission weight were declared failures and treated as a separate group. They were excluded from analysis.

Statistical analysis. One way analysis of variance was

Table 1 *Admission clinical data on the study children. Values are mean (SEM) except for sex and aetiology (No)*

	Treatment group		
	Glucose-ORS (n=24)	*Wheat-ORS (n=24)*	*Rice-ORS (n=24)*
Age (months)	40.1 (5.2)	48.6 (4.02)	48.5 (4.6)
Sex (M/F)	23/3	24/2	22/4
Admission body weight (kg)	10.2 (0.6)	11.2 (0.6)	10.9 (0.4)
Weight/height (% NCHS)	78 (2.8)	76 (30)	78 (2.6)
Weight/age (% NCHS)	63 (1.7)	64 (1.9)	63 (1.7)
Duration of diarrhoea before admission (hours)	14 (4.1)	15.4 (2.3)	15 (2.1)
Duration of vomiting before admission (hours)	21.8 (6.4)	18.4 (3.6)	15.3 (2.5)
Aetiology of diarrhoea (cholera/non-cholera)	19/7	20/6	20/6
Admission serum specific gravity	1.0320 (0.00003)	1.0316 (0.0004)	1.0306 (0.0004)
Admission packed cell volume (%)	41 (1.5)	40 (1.5)	38 (0.9)
Volume of initial intravenous treatment (ml/kg)	90 (5.3)	87 (7.8)	82 (5.9)

NCHS=National Center for Health Statistics performed to establish general significance between the three groups When significance was established Duncan's multiple range test was applied to detect differences between two groups.

Results

The admission clinical data of the study children are shown in Table 1. Patients in all three groups were comparable for sex, age weight, duration of diarrhoea and vomiting before admission, degree of dehydration, and fluid required for initial rehydration. Most of the patients in all three groups had cholera (Table 1) Except for two patients with shigellosis (one in the glucose-ORS group and one in the wheat-ORS group) the remaining patients had diarrhoea due to *E. coli* infection. The children receiving rice-ORS were, however, less dehydrated, as assessed by their admission serum specific gravity and packed cell volume value, compared with the other two groups, although the difference was not significant.

Twenty four hourly ORS intakes and purging rates in the patients with cholera are shown in Figure 1. There was a progressive decrease in stool volume in all the groups. Compared with patients receiving glucose-ORS, the other two groups had significantly decreased rates of purging at the first and second 24 hours ($p<0·01$). The glucose-ORS group, however, had significantly higher ORS intakes compared with the other two groups ($p<0·01$) during the first 24 hours. Similar observations were made between the groups in both ORS intake and stool output during the 48–72 hour period, although the difference was less significant ($p<0·05$).

In children with diarrhoea not due to cholera, however, no significant difference was observed at any interval between the groups with regard to ORS consumption and rate of purging (Fig. 2).

Table 2 provides additional information regarding duration of diarrhoea after admission to hospital,

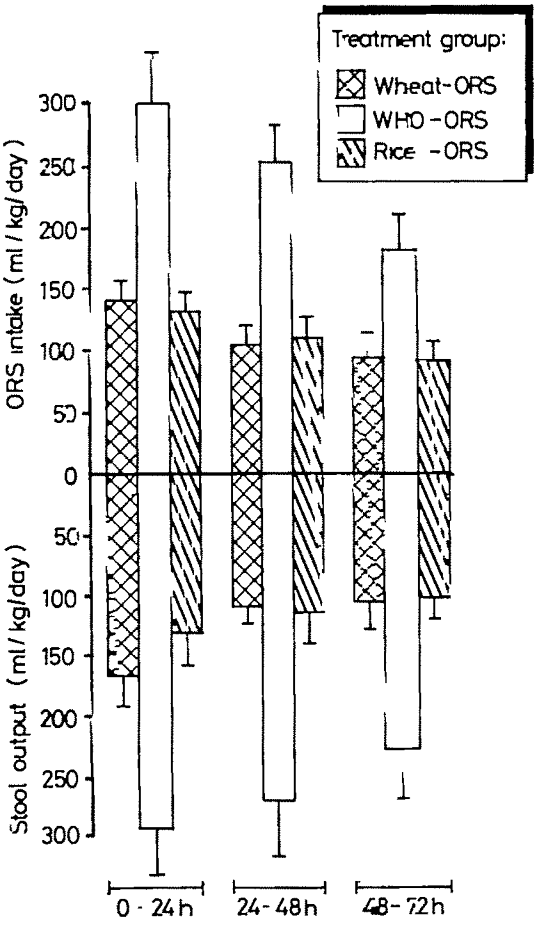

Fig. 1 *Mean (SEM) 24 hourly oral rehydration solution intake (ORS) and stool output in patients with cholera.*

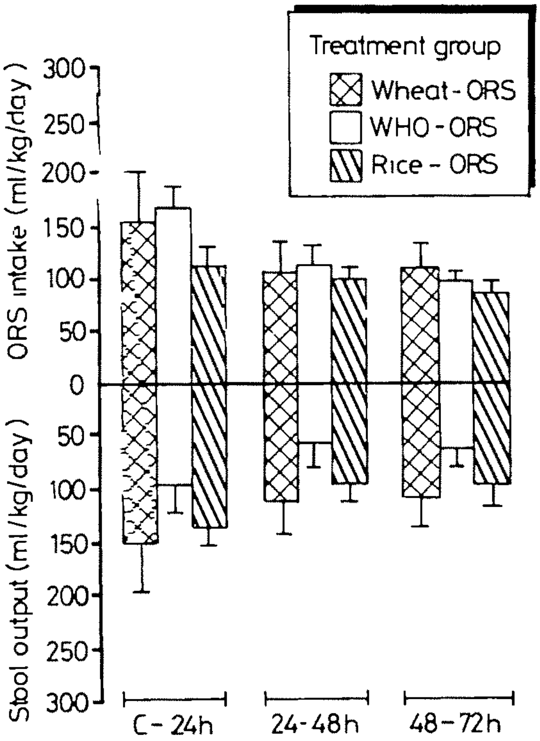

Fig 2 *Mean (SEM) 24 hourly oral rehydration solution (ORS) intake and stool output in patients without cholera*

Table 2 *Comparison of various characteristics after treatment with different oral rehydration solutions Values are mean (SEM)*

	Treatment group		
	Glucose-ORS	*Wheat-ORS*	*Rice-ORS*
Duration of diarrhoea after admission to hospital (hours)	90 (8 7)	80 (6 0)	78 (5 8)
Sugar content in stool after hydrolysis (mmol/l)			
24 h	11 2 (4 5)	10 0 (5 9)	12 7 (5 5)
48 h	12 2 (3 6)	9 3 (4 5)	15 3 (3 8)
72 h	15 5 (3 5)	10 4 (2 8)	16 0 (2 7)
Urine output (ml/kg/day)			
24 h	32 8 (7 6)	65 3 (8 8)	60 3 (6 3)
48 h	42 9 (6 6)	37 4 (7 0)	45 5 (6 7)
72 h	47 6 (9 9)	46 5 (7 5)	43 6 (5 9)
Weight gain			
24 h	7 0 (1 0)	7 3 (1 2)	6 5 (1 2)
48 h	7 0 (1 5)	6 9 (1 6)	6 0 (1 5)
72 h	8 0 (1 0)	7 6 (1 3)	6 0 (1 7)

sugar content in stool after hydrolysis, 24 hourly urine output, and percentage weight gain in the three groups. Sugar content after hydrolysis in the wheat-ORS group was lower compared with the other two groups, although the difference was not significant. Duration of diarrhoea after admission to hospital was comparable in all three groups. Urine output was significantly less in patients receiving glucose-ORS compared with the other two groups during the first 24 hours ($p<0{\cdot}05$). Children receiving wheat-ORS and glucose-ORS had, on average, gained more weight at the time of discharge than the children receiving rice-ORS, but the difference was not significant. There were six therapeutic failures (as described above), two in each of the groups. All six patients had positive results of culture for cholera on admission, with severe dehydration (mean specific gravity=1·0330) and vomiting during the early period of rehydration.

Discussion

This study shows that hydrolysed wheat-ORS, like rice-ORS and glucose-ORS, can be used effectively in the treatment of cases of acute diarrhoea. Both of the cereal based ORS were found, however, to be superior to glucose-ORS, considering the decreased rate of purging as well as consumption of ORS

The carbohydrate of cereals is predominantly starch, and it is speculated that this starch is digested by intraluminal enzymes, slowly releasing the glucose molecules that stimulate optimum absorption of sodium without imposing an 'osmotic penalty'. In a recent study a significant reduction of both stool volume (about 50%) with less intake of ORS was observed by using 80 g rice powder to replace sucrose or glucose in the standard electrolyte solution.[7] In another recent study wheat extract mixed with milk was found to be effective in the management of severe diarrhoea in malnourished children after initial rehydration.[14] No untoward effects—for example, osmotic diarrhoea, hypernatraemia, etc—were observed after the intervention.

We attempted to ensure that this study comprised mainly patients with acute watery diarrhoea. Of these patients with diarrhoea not due to cholera, however, all had infection with enterotoxigenic *E. coli*, except for two with shigella infection (one each in the rice-ORS and wheat-ORS groups). Wheat extract used in this study was partially hydrolysed, resulting in a lower sugar content in the stool after hydrolysis. Urine output was significantly lower during the last 24 hours of treatment in patients receiving glucose-ORS compared with those receiving wheat-ORS This may have been due to an increased rate of purging in the glucose-ORS group. Less weight gain in the rice-ORS group may be explained by the fact that they were initially less dehydrated and had less intake of ORS.

It is believed that the incidence of gluten enteropathy may increase with the use of wheat products, though in our limited study diarrhoea was not aggravated in any of our patients by the use of the wheat solution.

In developing countries acute diarrhoea leads in many children to both fluid-electrolyte malnutrition and protein energy malnutrition. Glucose polymers are known to be powerful carrier molecules of sodium and water absorption in healthy subjects. Converting any starch (like wheat in this study) into soluble carbohydrates, the preparation of ORS will be simple. It may also be possible to formulate ORS that is energy dense and facilitate early rehabilitation of malnourished children with diarrhoea. This study illustrates that an oral solution of electrolytes and wheat extract could maintain fluid and electrolyte balance in patients with acute dehydrating diarrhoea. Cereal based ORS has been found to be superior to glucose-ORS. All the cereal ORS preparations so far tested, however, need boiling and are suitable for use as a home solution in cases of diarrhoea. This is the first cereal product that can be used as cold water preparation and therefore has the prospect of being available in packet form, although the cost of extract preparation may be a constraint.

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Effects of feeding and social factors on diarrhoea and vomiting in infants

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SUMMARY In a prospective study of infants and their feeding in south east Queensland, Australia, the incidences of reported diarrhoea and/or vomiting in breast, bottle, and mixed (breast and bottle) fed infants were compared from birth to 1 year. Up to 6 months infants who were given breast feeds, with or without other milks, had less diarrhoea and/or vomiting than those given bottle feeds only Breast feeding seemed to protect the infant against possible introduced infections even when other milks were given along with the breast milk. After 6 months breast feeding did not reduce the incidence of gastrointestinal infection. In both upper and lower social class families infants given solids before 3 months had less diarrhoea and/or vomiting than those given solids later. Bottle fed infants aged 3–6 months in upper social class families had fewer gastrointestinal problems than those of lower social class families. This study suggests that up to the age of 6 months, in this population, breast feeding protects the infant against diarrhoea and/or vomiting, but other milks and solids can safely be given to supplement the breast milk. Breast feeding conferred no significant protection after 6 months.

Mothers are encouraged to breast feed their infants.[1] In developed Western countries some studies,[2 3] but not all.[4–6] have shown that the incidence of diarrhoea and/or vomiting (D/V) is lower in breast fed infants compared with those not receiving breast milk. Lower respiratory tract and ear infections are also reduced,[2 7 8] but upper respiratory tract infections are not.[9] In Western countries the trend back to breast feeding has been led by upper and middle social class mothers.[10–12] Through better environment and hygiene, these upper and middle class families already have lower rates of infection than lower class families.[9 13] It is therefore necessary to separate clearly the benefits of breast feeding from those of social class.

Sooner or later, other foods and milks must be given to a breast fed infant.[14] With such foods comes the risk of bacterial and other infections.[15 16] Once these foods are introduced, should the mother continue to breast feed and, if so, for how long?

We have studied this problem on a group of Australian mothers and their infants to determine which factors contribute to D/V in these infants and the measures that the mothers can take to minimise the risk

Patients and methods

Brisbane and Ipswich are subtropical cities in south east Queensland, with populations of 1 000 000 and 80 000 people, respectively. Mothers of infants born in 1984 who attended maternal and child health clinics in four centres in these two cities were asked if they would participate in a one year prospective study on the growth and feeding of their infants. The clinics were selected to cover the range of social classes. Mothers were interviewed for a year at roughly monthly intervals from the time their infants were about 1 month old

At the first interview the mothers were asked their husbands' occupations and other information about their families. During the first and at each subsequent interview, the mothers were asked if their infants had had any feeding or health problems since the last interview and, if so, what treatment was given and who advised this treatment. Mothers were asked if they were breast, bottle, or mixed (breast and bottle) feeding their infants and if they gave them foods other than milk.

In these analyses the ages of the infants have been divided into 0–3, 3–6, 6–9, and 9–12 months. For each of these periods, the infants were included in the results for these months if they continued to participate in the study throughout the three month period. Of 173 infants recruited into the study, about 25% dropped out before the infants were a year old, either in the first two or three months or later because the families moved to another area.

Infants were considered to have diarrhoea and/or vomiting (D/V) if their mothers at one of the monthly interviews said that their infants had required treatment for this problem. The data from each monthly interview were combined into three monthly intervals (+ two weeks). Each infant was counted only once, even though he may have had more than one attack of D/V in the three months. Infants were not considered to have D/V if they possetted after feeds or if they had D/V but their mother took no specific action.

The milk feeds of infants over each three months were recorded as either (1) breast fed only, (2) bottle fed only, (3) mixed (breast and bottle) fed, or (4) weaned, if breast milk was stopped and replaced with bottle feeding in the three month interval. The giving of solids did not affect this classification. Infants were counted as having solids in the preceding months if at any time in that period they were given solids.

The husbands' occupations were used as indicators of social class, using the Congalton Australian classification.[17] The grades of this classification are professional=1, managerial and business=2, office and sales=3, farmers and technicians=4, skilled workers=5, semi-skilled workers=6, and unskilled workers=7. In the analyses social class was divided into upper (grades 1–4) and lower (grades 5–7) social classes. To test the effect of parity, mothers were divided into para 1 and para 2+.

Data were compared by simple tabulation with the χ^2 test or Fisher's exact test and by using a multi-way, non-parametric method that separated the effects of the different factors in a multi-factorial situation and tested the independent significance of each factor.[18 19]

Results

Pattern and treatment of diarrhoea and/or vomiting (D/V). Altogether, 173 infants were enrolled in the study. Of these, 123 were seen for the full year. Sixty six (54%) of these 123 infants had one or more episodes of D/V in their first year (Table 1). Most of the D/V was minor. Only three infants were admitted to hospital for D/V and none died. These three infants were all less than 6 months old and were either bottle fed or weaned.

The overall patterns of D/V related to social class, milk feeding, and age of infant are shown in the Figure. Diarrhoea and/or vomiting was most

Table 1 *Numbers of infants with diarrhoea and/or vomiting (D/V) between 0–3, 3–6, 6–9, and 9–12 months. The mother's source of treatment was an indication of the severity of D/V*

	Age of infant (months)			
	0–3	*3–6*	*6–9*	*9–12*
Total No of infants	143	137	129	123
No of infants with D/V treated by				
Mother	2	5	5	9
Nurse	4	4	0	0
Doctor	11	14	15	25
Hospital	2	1	0	0
Total No (%) with D/V	19 (13)	24 (18)	20 (16)	34 (28)

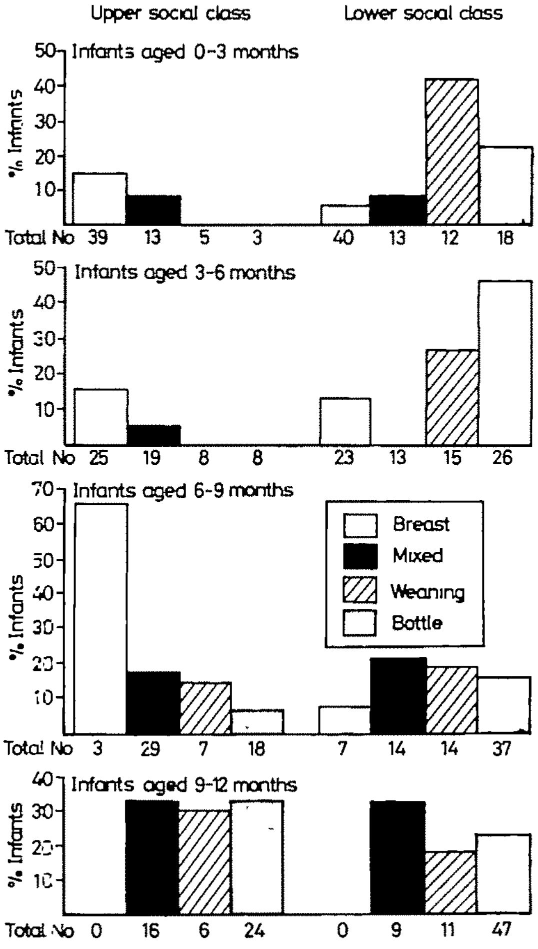

Figure *Percentage of infants with diarrhoea and/or vomiting by age of infant, type of milk feed, and social class* common in infants aged 9–12 months. The Figure shows that up to 6 months infants from lower social class families generally had more D/V than those from upper social class families. After the age of 6 months the effect of social class disappeared. For infants aged 6–9 months, the incidence of D/V in breast fed infants seems high, but there were only three infants in this group, so the difference in the incidence of D/V with various feeding regimens was not significant.

The type of feeding, social class of the family, and parity of the mother may all affect the incidence of D/V in the infant at any age. Multi-factorial analyses were used therefore to isolate the effects of each factor.[18 19] In the following analyses only infants either breast, bottle, or mixed fed throughout for each three month period have been included (Table 2; more detailed tables are available from the authors on request).

Between birth and 3 months, it was found that the proportion of infants with D/V did not differ significantly between those who were breast fed and those who were mixed fed (breast 10%, mixed 8%), but infants who were bottle fed had significantly more D/V than those mixed fed (bottle 20%, mixed 8%; p=0·03). Social class and parity had no effect. Infants given solids before 3 months had less D/V than those not given solids (solids 5%, no solids 16%; p=0·003). This unexpected finding was present separately in upper and lower social classes and for all types of milk feeding. (The percentage incidences given in the text make no allowance for other factors that may influence the incidence of D/V.)

A similar analysis was performed for infants aged 3–6 months The multi-way median test found no significant differences in the proportion of infants with D/V between those who were breast fed and those who were mixed fed (breast 15%, mixed 3%), but infants who were bottle fed had significantly more D/V than those who were mixed fed (bottle 35%, mixed 3%; p=0·005). Overall, the social class of the family had no effect, but among the bottle fed infants those from the lower social classes had more D/V than those from the upper social classes (lower social class 4/18, upper social class 0/3; Fisher's exact test, p=0·01). The parity of the mother had no effect (para 1 17%, para 2+ 18%). Breast fed infants given solids by 6 months had less D/V than those who were not given solids (solids 16%, no solids 50% (2/4); p=0·01).

For infants between 6 and 9 months, the overall incidence of D/V was 16%. The multi-way median test showed no significant differences in the proportion of infants with D/V when breast fed infants were compared with mixed fed infants or when mixed fed infants were compared with bottle fed infants. Social class of the family and parity of the mother had no effect. All infants received solids by 9 months.

By 1 year all infants received non-breast milks, although some were still breast fed Between 9 and 12 months the overall incidence of D/V was 28%. There were no significant differences in the proportion of infants with D/V between the mixed and bottle fed groups. Social class of the family and parity of the mother had no effect.

Discussion

Under the age of 6 months infants given only formula or cow's milk feeds had significantly more

Table 2 *No (%) of infants with diarrhoea and/or vomiting (D/V) between 0–3, 3–6, 6–9, and 9–12 months by type of milk feeding and giving of solids*

Infants' age	*Solids*								
	Given				*Not given*				
	Milk feed								
	Breast	*Mixed*	*Bottle*	*Subtotal*	*Breast*	*Mixed*	*Bottle*	*Subtotal*	*Total*
0–3 months									
Total No	23	14	20	57	56	12	1	69	126
No (%) with D/V	0 (0)	0 (0)	3 (15)	3 (5)	8 (14)	2 (17)	1 (100)	11 (16)	14 (11)
3–6 months									
Total No	44	32	34	110	4	0	0	4	124
No (%) with D/V	5 (11)	1 (3)	12 (35)	18 (16)	2 (50)	—	—	2 (50)	20 (18)
6–9 months									
Total No	10	43	55	108	0	0	0	0	108
No (%) with D/V	2 (20)	6 (14)	8 (15)	16 (15)	—	—	—	—	16 (15)
9–12 months									
Total No	0	24	71	95	0	0	0	0	95
No (%) with D/V	—	8 (33)	19 (27)	27 (28)	—	—	—	—	27 (28)

D/V than those who received breast milk only or a combination of breast and bottle feeds. Infants who received both breast and bottle feeds had no more D/V than those who received breast milk only. These findings indicate that, in the group studied, the absence of breast milk influenced the incidence of D/V and the presence of other milks did not. Put another way, the protective effects of breast milk[20,21] lowered any susceptibility to infection induced by other milks. After 6 months breast milk brought no significant protection against D/V. We still have no explanation for the significantly protective effect of solid food given in the first six months. The same observation was made in a similar study in Chile[22] but not in a study in New Zealand.[3]

These findings have practical implications for mothers and infants in a Western environment. Although D/V is common it is seldom severe, so the health penalties of bottle feeding are not great. If a mother wants to breast feed but cannot meet the needs of her infant, however, then this study shows that complementary bottle feeds do not increase the risk of D/V, while solid foods may lower the risk

It would be potentially dangerous to extrapolate these findings uncritically to other countries and communities. In some developing countries where the nutrition of the mother and infant are poor mothers may traditionally at an early age, supplement their breast milk with feeds of gruel, other milk, or foods. Such practices are perceived to maximise the benefits to the mother and the infant. The supplementation of breast milk with other foods may carry both high gains in nutrition and high risks of D/V where environmental contamination is heavy. In this study giving supplementary foods to breast fed infants less than 6 months old did not increase the risk of D/V There is a need to evaluate scientifically, in developing countries, the risks of D/V against the benefits of such feeding practices in the maintenance of infants' health, including adequate nutritional state.

Note

Only summary tables of the data have been included in this paper The Venn diagrams, which give the detailed data and have been used in the multifactorial analyses are available from AED

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Gastric emptying with gastro-oesophageal reflux

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SUMMARY The time taken for gastric emptying of a liquid (milk) or a semi-liquid (pudding) meal was evaluated in 477 infants and children. These patients were referred for suspected gastro-oesophageal reflux and underwent gastro-oesophageal scintigraphy, prolonged oesophageal pH study, manometric evaluation of the lower oesophageal sphincter pressure, and fibreoptic endoscopy. No difference in gastric emptying was observed in children aged under 3 years, regardless of the presence or absence of the gastro-oesophageal reflux, the pressure of the lower oesophageal sphincter, or the presence of oesophagitis. In children over 6 years, however, gastric emptying was significantly delayed in those presenting with reflux compared with those without reflux; in children over 3 years there was slower gastric emptying in those with a decreased lower oesophageal sphincter pressure compared with those with higher pressure and in those with overt oesophagitis compared with those without oesophagitis. This study suggests that gastro-oesophageal reflux is more severe in childhood than in infancy, probably due to more complex motor disorders affecting the gastric fundus as well as lower oesophageal sphincter function.

Several techniques are currently available for measurement of gastric emptying of a liquid or semi-liquid meal, such as the marker dilution technique,[1] radiological studies,[2] radioisotopes,[3] and, more recently, ultrasound scanning [4] It has been shown that gastric emptying is delayed in infants with congenital heart disease[5] and with respiratory distress syndrome,[6] while it seems to be accelerated when pancreatic insufficiency is present.[7] There is some controversy, however, about the evaluation of the time taken for gastric emptying in infants and children who present with gastro-oesophageal reflux· some authors have found significantly delayed gastric emptying in children with reflux,[8 9] while others have not.[10-12]

We have reviewed about 500 gastro-oesophageal scintiscans performed in our department during the last five years, firstly, to compare the time taken for gastric emptying in children with and without gastro-oesophageal reflux and, secondly, to assess whether delayed time for gastric emptying to take place could be associated with decreased lower oesophageal sphincter pressure with or without concomitant reflux peptic oesophagitis.

Patients and methods

A total of 477 infants and children referred with symptoms that suggested gastro-oesophageal reflux (vomiting or regurgitation, or both, 64%; recurrent pulmonary disease, 21%; near miss 'sudden infant death syndrome', 10%; retrosternal pain, 5%) were investigated. Gastro-oesophageal scintigraphy was performed in all of them. In addition to this radionuclide investigation, 89 were also studied by means of 24 hour continuous oesophageal monitoring of pH, 202 underwent fibreoptic endoscopy for diagnosis of oesophagitis, and 188 had manometric evaluation of the lower oesophageal sphincter pressure

The series of 477 patients was subdivided in six groups according to age: (1) less than 3 months (mean 1·8 months), (2) 4 to 6 months (mean 4·9 months), (3) 7 to 12 months (mean 8·9 months), (4) 13 to 36 months (mean 20·9 months), (5) 3 to 6 years (mean 4·4 years), and (6) 7 to 14 years (mean 11·2 years). As a result of the smaller number of patients investigated the results of pH study, endoscopy, and manometry were analysed in five age groups (groups 5 and 6 were considered together).

Gastro-oesophageal scintigraphy. The technique of gastro-oesophageal scintigraphy has been well described.[13] In our department a large field scintillation camera (Toshiba) and a mini-computer Simis 3 (Informatek) were used. A 7·4 MBq dose of ^{99m}Tc sulphur colloid was mixed with a small amount of the usual meal and given orally. The rest of the meal was given immediately after to wash down the remaining radioactivity in the mouth. The meal consisted of the usual milk formula for children aged under 1 year or pudding for those 1 year or over.

The patient was allowed to belch and then placed in supine position over the detector for a recording period of one hour, using 20 second frames. Regions of interest were drawn over the oesophagus and stomach and the time activity curve of the oesophagus was obtained and expressed as a percentage of the gastric activity. Each reflux peak was checked by inspecting the corresponding image to exclude artificial peaks due to gastric displacement into the oesophageal area. The number, intensity, and duration of the reflux peaks were noted and a reflux index calculated by taking these three variables into account.[14]

The number of counts over the gastric region of interest was measured during the one hour recording, allowing estimation of the time taken for gastric emptying. We used the residual gastric activity at 60 minutes expressed as a percentage of the initial activity (R60) as the variable. We chose this variable in preference to the half life of the radioactive isotope ($T_{½}$) because R60 does not require an a priori hypothesis concerning the shape of gastric emptying curve.

pH study. Continuous 24 hour oesophageal pH was monitored using a flexible MI-506 glass pH probe (Microelectrode Inc), the distal end being placed at 87% of the total distance from the nares to the lower oesophageal sphincter. pH was determined continuously and the data, recorded every 7·5 seconds, were stored into a portable system (Memolog 600-Novo) and processed with an Apple IIe computer, using our own program. An oesophageal pH under 4 was regarded as abnormal. Each episode of reflux was analysed and the reflux index (percentage of total time of oesophageal pH inferior to 4) was considered to be abnormal when greater than 5.

Oesophageal manometry. A three lumen tube assembly was employed to study oesophageal motility. The recording catheters were arranged to measure pressure through side orifices, spaced at 2·5 cm intervals. Each pressure catheter was infused with distilled water by a syringe pump at a rate of 0·8 ml/min. Resistance to infusion was transmitted to external Statham transducers. The pressure profiles were continuously recorded with a multichannel polygraph recorder. The resting lower oesophageal sphincter pressure in each patient was measured by the pull through technique.[15] No premedication was used to perform this examination.

Oesophagoscopy and histology. Endoscopic examination was performed with paediatric fibreoptic panendoscopes (Olympus GIF-XP, GIF P-10). Two or more biopsy specimens were obtained using conventional endoscopic biopsy forceps either from an area where lesions were evident or 2–3 cm above the squamocolumnar junction if the mucosa seemed to be normal. If there were obvious oesophageal ulcers no biopsy specimen was taken. All specimens were reviewed by a pathologist. A classification of the histological findings was made on the basis of the following criteria:

(a) Normal biopsy;

(b) Oesophagitis grade 1 (hyperplasia of the epithelium, vascular papillae extending more than two thirds to the free luminal margin, ingrowth of vessels in the vascular papillae);

(c) Oesophagitis grade 2 (abnormal infiltration of neutrophilic or eosinophilic polymorphonuclear leucocytes, or both);

(d) Oesophagitis grade 3 (erosion or complete ulceration of the mucosa, columnar lined oesophagus).

This series of examinations was performed for each child during a period ranging from two to seven days.

Statistical analysis. Statistical analysis was carried out by the non-parametric Wilcoxon rank sum test.

Results

The total population of 477 patients was divided into two groups, those with and those without reflux, on the basis of the results of scintigraphy or pH study, or both. Group 1 was formed of the 291 children who had abnormal results in at least one of these two examinations. Group 2 was formed of the 186 children with normal results.

The comparison of the time taken for gastric emptying in these two groups of patients is presented in Figure 1. A significant difference ($p<0·001$) was found only in the children over 6

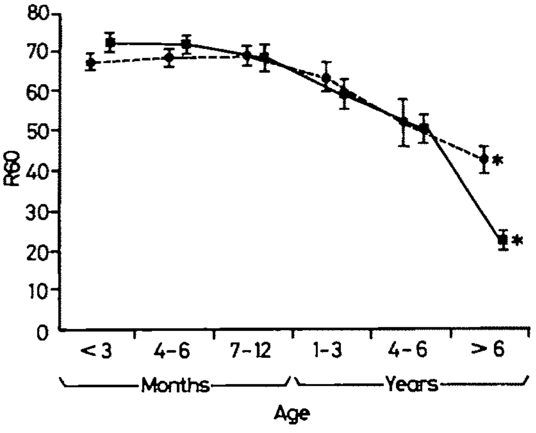

Fig 1 *Mean (SEM) of age related R60 (residual activity in the stomach after 60 minutes) relation with gastro-oesophageal reflux (●- - -● = those with reflux; ■——■ = those without reflux)*

*p<0·001

Table *Mean (SEM) age related R60 (residual activity in the stomach after 60 minutes) in patients with normal and abnormal results of gastro-oesophageal scintigraphy and pH study*

	Age group					
	<3 months	*4–6 months*	*7–12 months*	*1–3 years*	*4–6 years*	*>6 years*
Scintigraphy results						
Normal	65·5 (1·4)	68·0 (1·7)	68·9 (2·6)	64·2 (3·4)	51·0 (5·0)	44·2 (4·5)*
Abnormal	70·6 (2·3)	71·2 (1·7)	70·2 (2·8)	60·5 (3·7)	53·0 (4·5)	25·1 (2·5)*
pH study						
Normal	61·7 (4·0)	67·5 (4·9)	70·2 (4·4)	77·7 (4·2)	47·0 (6·5)**	
Abnormal	68·9 (4·3)	70·5 (5·7)	74·5 (5·0)	58·8 (10·0)	26·2 (5·3)**	

$^*p<0·005$, $^{**}p<0·05$

years, gastric emptying being delayed in patients with reflux (mean (SEM) R60: 41·6 (3·8) in those with reflux *v* 23·7 (2·8) in those without reflux). A further comparison of R60 between those with and those without reflux was performed by analysing separately the results of pH study on one hand and of reflux scintigraphy on the other. No difference was observed between the two populations, except for the oldest subgroups (Table).

The lower oesophageal sphincter pressure, determined in 188 children, was >12 mm Hg in 119 patients and ≤12 mm Hg in 69. No significant difference in gastric emptying was found in children under 3 years with low and normal lower oesophageal sphincter pressures (Fig. 2). The difference was significant, however, in children over 3 years (mean (SEM) R60: 55·5 (6·6) in children with low pressure *v* 29·4 (5·9) in children with normal pressure, p<0·05).

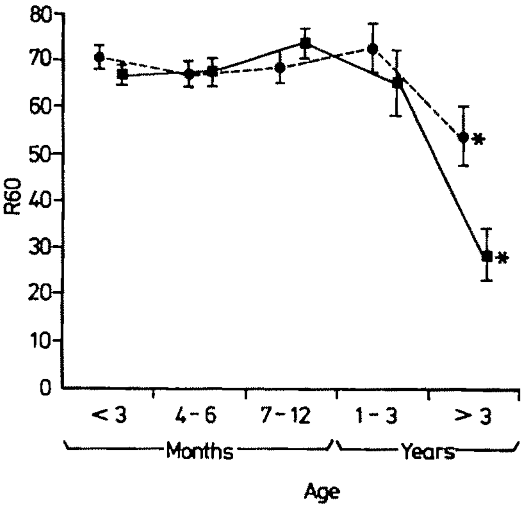

Fig 2 *Mean (SEM) of age related R60 (residual activity in the stomach after 60 minutes): relation with values of lower oesophageal sphincter pressure (●– – –● = those with lower oesophageal sphincter pressure ≤12 mm Hg, ■——■ = those with lower oesophageal sphincter pressure >12 mm Hg)*

*p<0·05

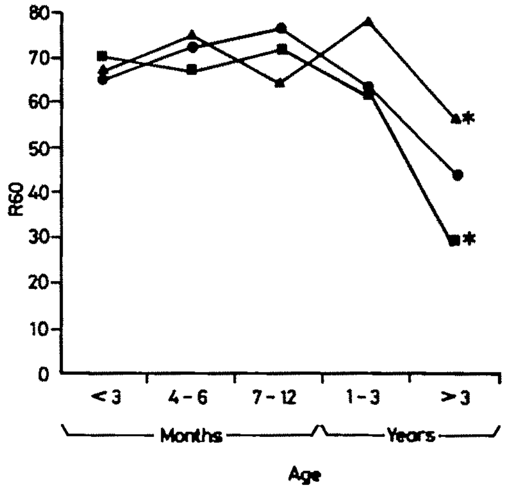

Fig 3 *Mean of age related R60 (residual activity in the stomach after 60 minutes): relation with endoscopical and histological findings (■——■ = those with normal findings, ●——● = those with oesophagitis grade 1; ▲——▲ = those with oesophagitis grades 2 and 3)*

*p<0·05

Endoscopic and histological findings were available for 202 children: there was no oesophagitis in 108 children, slight oesophagitis (grade 1) in 64, and overt oesophagitis (grades 2 and 3) in 30. Only in the oldest age matched subgroups was a significant difference in gastric emptying found between the children with overt oesophagitis and those without oesophagitis (mean (SEM) R60: 53·4 (7·8) *v* 30·4 (4·1); p<0·05) (Fig. 3).

Discussion

Since the very first studies of Cannon[16] many data have been published about gastric emptying in humans. Among the techniques currently used, scintigraphy with ^{99m}Tc [3] is a suitable method for the study of gastric emptying of a liquid or a semi-liquid meal. It is more physiological and better accepted than the marker dilution technique and its radiation hazard is less than the conventional radiological method. As a matter of fact, using 7·4 MBq of ^{99m}Tc sulphur colloid, the total body absorbed dose is less than 0·05 mGy and the gonadal dose is less than 0·2 mGy.[17] This exposure is less than a tenth that of conventional barium meal.[18]

Most of the previous studies have been performed in adults, whereas the mechanisms of gastric emptying in childhood have been investigated only recently, although the motor behaviour of the stomach seems to be altered in many childhood diseases. Unfortunately, because of the differences in the techniques used and in the ages of the patients investigated, previously reported data are not always comparable. It has been shown, for example, that the patterns of emptying of a liquid, a digestible solid, or an indigestible solid are different.[19] It has become clear that tonic fundal activity is mainly responsible for the emptying of liquids, while the distal stomach is much more concerned with the elimination of solids from the gastric cavity.[20]

Osmolality and fat composition,[21] protein,[22] and amino acid[23] contents of the ingested meal have an important influence on gastric emptying and often the different nutrients chosen by different authors for evaluating gastric emptying make comparison of their results difficult. It should also be emphasised that some technical problems may be related to the use of milk: when milk reaches the stomach there is a precipitation of casein, the radiotracer is sequestered into this fraction, and the time taken for gastric emptying describes mainly the emptying of the casein phase.[24] This could explain the low emptying rates found in infants when milk was used as a meal using scintigraphy. Another source of controversy is the variable employed to express the rate of gastric emptying. In our experience fitting a straight line to the gastric time activity curve, to measure the half time of gastric emptying, seems to be a questionable technique. When using milk formulas the pattern of gastric emptying is variable, a sudden decrease of activity being preceded or followed by periods during which no emptying is observed at all. For that reason, we preferred to use the residual gastric activity after 60 minutes as the variable. In this study we used milk in children under 1 year because it represents the physiological meal at this age.

To evaluate the gastric emptying of children with suspected gastro-oesophageal reflux, our population was subdivided into two groups, those with reflux and those without reflux, according to the results of gastro-oesophageal scintigraphy and prolonged pH study, these two techniques being considered as the most reliable methods for the detection of reflux disease.[14 25]

A significant delay in the time taken for gastric emptying was found only in those children over 6 years with reflux. Whatever the technique used for the diagnosis of reflux (pH study or scintigraphy), no difference was seen in the time taken for gastric emptying of children, with or without reflux, in the lower age groups. A significant difference between those with and without reflux was observed from the age of 3 years, when pH study was used as the only criterion for the diagnosis of reflux, and from the age of 6 years when only scintigraphy was used. This difference might be due to the fact that the criteria that we have chosen for diagnosis of reflux by pH study were more selective and picked up patients with a more severe reflux disorder.

The delay in emptying of a liquid or semi-liquid meal is mainly due to abnormal gastric fundal function.[26] A delay in gastric emptying occurred in those children over 3 years with low lower oesophageal sphincter pressures, one of the major pathogenetic factors in patients with reflux.[27] Lower oesophageal sphincter and fundus can probably act as a synergic functional unit, both showing a relaxation reflex in response to swallowing, which is almost entirely mediated by the non-adrenergic, non-cholinergic nerve fibres.[28] Our findings that important abnormalities of the lower oesophageal sphincter can be associated with altered gastric emptying support the concept of an interrelation between lower oesophageal sphincter and fundic function.

In infants no correlation was found between oesophagitis and gastric emptying. These data are consistent with those of Baulieu, who found normal gastric emptying in very young children with reflux oesophagitis.[9] The findings that older children with obvious oesophagitis also have a slower rate of emptying of the stomach agrees with the increasing severity of the reflux disease with age, the fundal function seeming to be affected as well.

It has been shown in adults that this disease can be part of a more complex disorder in which the gastrointestinal tract distal to the oesophagus may also be involved. McCallum *et al* showed an abnormal motor function of the stomach in a high percentage (41%) of adult patients with reflux,[29] and Behar and Ramsby showed an antral dysmotility in reflux oesophagitis.[30] After the first few years of life children probably develop reflux disease, therefore, that resembles the adult form more, with a motor disorder not always confined to the lower oesophageal sphincter but that also involves other upper gastrointestinal structures.

The evidence that delayed gastric emptying can be significantly associated with a low lower oesophageal sphincter pressure and with a severe reflux oesophagitis strongly supports the role of prokinetic drugs, which can enhance the emptying of the stomach, in the treatment of reflux disease.

To our knowledge, this paper is the first report to compare gastric emptying in children, with and without reflux, and evaluates a large series of patients according to their age. Rosen *et al* have studied gastric emptying using a 5% dextrose solution in two groups of children, those under and those over 2 years of age.[10] They found no difference in children with or without reflux. Our data, even if we used another meal, are not significantly different from those of Rosen: if the patients of the different subgroups above 2 years are considered together, the difference for the older children (>6 years) is masked and no difference can then be shown between those with and without reflux.

On the other hand, Hillemeier *et al* claimed that in infants with reflux complicated by failure to thrive or recurrent pulmonary disease, or both, gastric emptying was slower than in controls.[8] These data are not incompatible with our own as, unlike in Hillemeier's patients, severe complications were seldom observed in our population.

Our study also shows a correlation between the age of the patients investigated and the rate of their gastric emptying, older children showing a faster emptying than younger children. Part of the difference can, of course, be explained by the change of meal (pudding) given to the older children. The age related differences are also obvious, however, comparing children aged 1 to 3 years, 4 to 6 years, and older than 6 years, who all received the same type of meal. The evaluation of the gastric emptying in children should therefore take into consideration the age of the patient investigated as well as the type of meal used for the study.

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Cisapride for gastro-oesophageal reflux and peptic oesophagitis

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SUMMARY Twenty children (age range 75 days–47 months) with reflux oesophagitis entered a random double blind trial in which they received either Cisapride (Janssen Pharmaceutical Ltd), a new prokinetic agent, or an identical placebo syrup. Diagnosis of gastro-oesophageal reflux was made by measurement of intraluminal oesophageal pH combined with manometry. Oesophagitis was assessed in all patients by histological examination of mucosal specimens taken during oesophagogastroduodenoscopy. Manometry, pH test, and endoscopy with biopsy examination were repeated at the end of the treatment period. Seventeen patients completed the trial, eight of whom were taking the drug and nine the placebo. Mean total clinical score and post-prandial reflux time (% of reflux) significantly improved in patients in the group given Cisapride but not in the group given placebo. Furthermore, there was a significant improvement of the histological oesophagitis score only in the children in the group given Cisapride, whereas placebo was ineffective. It is concluded that Cisapride is a useful agent both for the relief of symptoms of gastro-oesophageal reflux and for the healing of peptic oesophagitis in infancy.

In the past few years there have been a number of studies on gastro-oesophageal reflux in children.[1–3] Interest has been concentrated mainly on the clinical presentation and on providing reliable diagnostic tests. A few studies, however, have been directed towards assessing the therapeutic approach of the disease. Recent trials have shown that children with reflux can be successfully treated with bethanechol chloride,[4–7] a cholinergic drug that stimulates intestinal smooth muscle contraction.[8] In a controlled trial antacids as well as cimetidine proved to be effective for the relief of both symptoms and oesophagitis.[9] Finally, a recent open study showed that domperidone, a new prokinetic agent, induced a significant improvement both in symptoms of reflux and in some gastro-oesophageal motility variables.[10]

In only one study, however, was the trial designed in a double blind fashion.[4] As gastro-oesophageal reflux has a favourable natural history in children,[11] double blind controlled trials would seem to be advisable to assess the true place of medical treatment of reflux in children.

Cisapride (R 51 619, Janssen Pharmaceutical Ltd) is a new prokinetic drug that stimulates smooth muscle cell contraction of the gastrointestinal tract.[12] This prompted us to investigate the effect of oral Cisapride compared with placebo in the treatment of children with symptomatic gastro-oesophageal reflux and peptic oesophagitis.

Patients and methods

Twenty patients, nine boys and 11 girls, aged 75 days–47 months, with a diagnosis of gastro-oesophageal reflux and oesophagitis, were entered into a double blind trial to compare Cisapride syrup (1 mg/ml) at a dose of 0·3 mg/kg three times a day before meals with placebo syrup, which was identical to Cisapride in taste and appearance, taken at the same dose, over eight weeks. In each patient diagnosis of gastro-oesophageal reflux was based on pH-metric demonstration of acid reflux. Fibreoptic endoscopy and biopsy examination revealed oesophagitis in all 20 patients. Infectious, neurologic, metabolic, and renal disorders were carefully excluded. Abnormalities of the oesophagus, stomach, and duodenum were excluded by upper intestinal x ray examination. Parents gave informed consent and the study was approved by the ethical committee of our faculty.

Gastro-oesophageal reflux was detected by a five hour pH study, performed after ingestion of apple juice (15–20 cc/kg), with a pH of 4. A small flexible electrode (MI 506, Microelectrodes Inc, Londonderry, New Hampshire, United States of America), calibrated with buffers at pH levels of 7·0 and 4·0, was introduced nasally and located at 87% of the distance from the nares to the lower oesophageal sphincter previously determined by manometry. Gastro-oesophageal reflux was defined as a fall in intra-oesophageal pH below 4 for at least 20 seconds.

Manometry was performed by a triple lumen catheter with side recording orifices spaced 2·5 cm apart and perfused with bubble free water at a low compliance infusion system (Arndorfer, Med Spec Co, Greendale, Wisconsin, USA). The probe was initially located into the stomach and subsequently moved across the lower oesophageal sphincter 0·5 cm at a time, remaining at each station long enough to obtain a stable pressure recording. Lower oesophageal sphincter pressure was determined as mean pressure of the three orifices, with the gastric pressure as zero reference, taking the mid-respiratory value. Motor activity of the distal oesophagus was recorded by placing the distal side hole of the catheter immediately proximal to the lower oesophageal sphincter. Oesophageal waves were elicited by administering 2 ml of 5% dextrose. Only waves preceded by at least 30 seconds of silent motor activity in the oesophagus were taken into account. Amplitude of peristalsis (mm Hg) was measured by subtracting the mean resting oesophageal pressure from the peak of the waves. Both oesophageal manometry and pH study were performed during the same session after a two to three hour fast without sedation. Patients with diagnosis of reflux underwent upper endoscopy with a small fibreoptic endoscope (GIF PX Olympus).

Mucosal erythema or oedema were not considered to be reliable findings of oesophagitis. Endoscopic lesions, such as friability, exudate, erosions, or ulcerations, were considered to be important markers of oesophagitis. During endoscopy, biopsy specimens were taken from the oesophageal mucosa, irrespective of its appearance, and examined by a histopathologist, who was unaware of the endoscopic findings. The degree of oesophagitis was histologically defined as 'mild' if there was basal cell hyperplasia and extension of the papillae, 'moderate' if there was also an increased cellularity of the lamina propria, and 'severe' if there were also signs of mucosal ulcerations.

Blood counts, urinalysis, and determination of serum transaminase and alkaline phosphatase activities, and bilirubin, creatinine, and urea concentrations were taken before randomisation to either Cisapride or placebo. During the study, frequent assessments were made of severity and frequency of symptoms and drug use. Manometry, pH study, endoscopy, and biopsy examination were repeated within two days before the end of the trial for comparison with pretreatment data. At completion of the trial the patients were classified as 'cured' if clinical, pH-metric, and histological variables had normalised, 'improved' if at least one of these three variables had ameliorated, and 'unchanged' or 'worsened' if no improvement or worsening was observed, respectively. Throughout the trial, parents were provided with diary cards to keep a daily record of the symptoms and physical signs. A scoring system was used to evaluate symptoms and physical signs as well as oesophageal histology of the patients (Table 1).

Data were analysed using either Student's *t* test or rank sum non-parametric tests p Values <0·05 were considered significant.

Results

Three patients failed to complete the study and were withdrawn, two because of febrile upper respiratory infections and one who failed to take the drug continuously. Eight patients (age range 90 days–36 months) were treated with the drug and nine (age

Table 1 *Scoring system for symptoms or physical signs and for oesophagitis assessed by histology*

	Evaluation	*Score (points)*
Symptoms or physical signs		
Vomiting or regurgitation, or both (episodes/week)	None	0
	1–3	3
	>3<7	6
	>7	9
Pneumonia or asthma (episodes/two months)	None	0
	1	5
	>1	10
Apnoea (episodes/week)	None	0
	1	6
	>2<5	9
	>5	12
Haematemesis (episodes/two months)	None	0
	1–2	5
	>2	10
Heartburn, dysphagia (episodes/week)	None	0
	1–3	2
	>3<7	4
	>7	6
Weight/height ratio (centile)	>50th	0
	>25th<50th	1
	>10th<25th	2
	5th–10th	5
	<5th	10
Oesophagitis (histology)	Normal	0
	Mild degree	3
	Moderate degree	6
	Severe degree	9

range 75 days–47 months) with the placebo. The two groups were comparable for clinical and histological scores and for percentage of reflux time at the pH study.

Four patients on Cisapride and one on placebo were healed, two patients on Cisapride and one on placebo were considered to have improved, and nine children remained unchanged or worsened. Of these, two were in the Cisapride group and seven in the placebo group. As shown in Table 2, the post-treatment clinical score, percentage of reflux time, and histological score for oesophagitis were significantly better in the group treated with Cisapride but showed no change in the group treated with placebo Furthermore, at the end of the trial amplitude of peristalsis was significantly increased only in the Cisapride group, whereas lower oesophageal sphincter pressure and mean duration of episodes of reflux showed no significant change in either groups. The percentage improvement from the pre-study baseline in clinical score and duration of reflux was higher in the Cisapride group than in the placebo group (Figure) There was a significant difference, however, only for the percentage change of the clinical score.

Four patients on Cisapride (three with moderate and one with mild oesophagitis before treatment) were totally healed. Two of the remaining four patients on Cisapride had severe oesophagitis at the beginning of the study, one of whom remained unchanged and one of whom improved. The other two patients on Cisapride had moderate oesophagitis, and again one remained unchanged and one improved.

Of the patients on placebo, one who initially had severe oesophagitis remained unchanged at the completion of the trial. Six had moderate oesophagitis at the start of the trial. Of these, three failed to improve, two had an improvement in the histological appearance, and one healed. Finally, two patients who had mild oesophagitis at the start of the trial remained unchanged at the end.

No significant changes occurred in the biochemical variables. No untoward clinical signs or symptoms were observed during the trial.

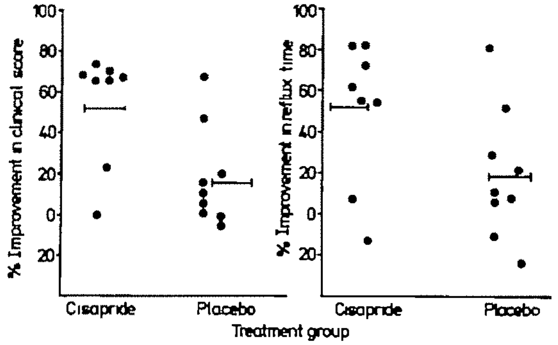

Figure *Percentage improvement from pre-study baseline in clinical and reflux time for each patient at completion of the double blind trial. Mean (SD) clinical score for the Cisapride group was 54.05 (27·69) and for the placebo group was 17·69 (22·64) (Student's* t *test, p<0·01; Wilcoxon rank sum test, p<0·05). Mean (SD) reflux time for the Cisapride group was 50 92 (36·7) and for the placebo group was 19·83 (30·7) (Student's* t *test, p=0·07, not significant; Wilcoxon rank sum test, p=0·11, not significant)*

Discussion

Major advances have recently been made in under-

Table 2 *Results obtained in 17 patients with gastro-oesophageal reflux after eight weeks of treatment with Cisapride or placebo Results are given as mean (SD)*

	Treatment group							
	Cisapride				*Placebo*			
	Before treatment	*After treatment*	*Student's* t *test*	*Signed rank test*	*Before treatment*	*After treatment*	*Student's* t *test*	*Signed rank test*
Clinical score*	16 25 (7 1)	7 87 (7 05)	p<0 01	p<0 05	13 5 (4 15)	10 8 (3 95)	NS	NS
% Of reflux time*	25 68 (11 65)	11 83 (11 07)	p<0 05	p<0 05	32 71 (18 35)	23 85 (13 57)	NS	NS
Duration of episodes of gastro-oesophageal reflex (min)	4 28 (0 71)	4 12 (1 11)	NS	NS	4 60 (0 98)	4 51 (1 0)	NS	NS
Lower oesophageal sphincter pressure (mm Hg)	20 62 (7 53)	19 62 (4 62)	NS	NS	20 55 (5 87)	22 22 (7 10)	NS	NS
Peristalsis amplitude (mm Hg)	46 9 (15 7)	57 7 (11 5)	p<0 05	p<0 05	49 92 (18·10)	50 07 (10 11)	NS	NS
Histological score for oesophagitis	6 37 (1 92)	3 0 (3 58)	p<0 05	p<0 05	5 66 (1 80)	4 33 (2 64)	NS	NS

*No significant difference in the two groups of patients for the clinical and histological scores and percentage of reflux time before treatment
NS=Not significant

standing the physiopathological mechanisms of gastro-oesophageal reflux.[13 14] There is evidence that the pathogenesis of reflux has many components, such as lower oesophageal sphincter incompetence, abnormal oesophageal peristalsis, delayed gastric emptying, and oesophageal mucosal damage from gastric content. Treatment of reflux might be directed, therefore, towards either counteracting upper gastrointestinal motor defects or altering the character of the gastric content available for reflux. Cisapride is a new prokinetic drug that facilitates release of acetylcholine from the myenteric plexus and has no dopamine blocking properties, and in vivo and in vitro studies have shown that it increases lower oesophageal sphincter pressure and amplitude of oesophageal peristalsis and improves gastric emptying (Gilbert RJ, Dodds WJ, Karhilas PJ, Hogan WJ, Lipman S Double-blind assessment of the effect of intravenous and oral Cisapride on oesophageal motor function. Abstract presented at First International Investigations Meeting on Cisapride, Brussels, December 1985.)[15] For this reason, the drug has great potential in the treatment of gastro-oesophageal reflux.

The results of this trial indicate that Cisapride is more effective than placebo in the relief of symptoms of gastro-oesophageal reflux in children. Symptomatic control in patients treated with Cisapride was documented both by decreased duration of reflux time during the repeated pH test and by significant improvement in the oesophageal histological damage. No changes in the lower oesophageal sphincter pressure were noted between the results of manometry before and after treatment in the two groups. Although the children on Cisapride showed a slightly significant increase of oesophageal peristaltic amplitude compared with those on placebo, however, amplitude of peristalsis was not remarkably decreased before treatment in either groups. Moreover, basal mean values of lower oesophageal sphincter pressure in all our patients were not different from that of a normal paediatric population.[16] This would suggest that patients included in the study as a whole had moderate reflux. Cisapride caused a significant reduction of the reflux time, whereas mean duration of reflux was unchanged. This finding was mainly due to a decreased frequency of episodes of reflux and implies that the drug might be more effective on the mechanisms related to the frequency of episodes of reflux, such as lower oesophageal sphincter pressure and gastric emptying. Cisapride has also been shown to improve gastric emptying: documentation of this effect is lacking in our study

Cisapride was also more effective than placebo in improving histological changes of oesophagitis. Of the 17 patients included in the study, however, only three had severe oesophagitis; the remaining 14 had mild or moderate oesophagitis The effectiveness of Cisapride in the treatment of more severe reflux oesophagitis remains to be proved.

The manometric findings, such as normal (or slightly decreased) pressure of peristalsis and lower oesophageal sphincter absence of non-specific oesophageal motor defects, and the prevailing moderate degree of oesophagitis, indicate that our group of selected patients was not seriously affected. It would be desirable, therefore, for future trials with Cisapride in children affected by gastro-oesophageal reflux to include more patients with severe reflux oesophagitis

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Controlled study of exclusion of dietary vasoactive amines in migraine

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SUMMARY To assess the effects of dietary vasoactive amines in the aetiology of childhood migraine, 39 children were randomly allocated to either a high fibre diet low in these substances or a high fibre diet alone. Both groups of children showed a significant decrease in the number of headaches and there was no significant difference between the two groups.

Dietary vasoactive amines have not been shown in this study to influence childhood migraine. The improvement seen in both groups emphasises the need for a control diet in studies designed to show that dietary manipulation improves disease.

Migraine is a common problem that affects some 4% of schoolchildren between the ages of 7 and 15 and often causes considerable distress and disruption of school and social activities.[1] The aetiology remains unknown and various dietary components and other stimuli have been considered to precipitate attacks in different individuals. Various foods contain vasoactive amines[2] and recent work has concentrated on biochemical idiosyncratic reactions to vasoactive amines[3-5] and on food allergy[6 7] as possible mechanisms for the suspected association between food intolerance and migraine.

Studies on the effect of vasoactive amines have produced conflicting results. Hannington's work in adults claimed to show that vasoactive amines were important precipitants of migraine,[2-4] but Forsyth could not confirm this in children.[5] These studies involved challenges with capsules that contained placebo or vasoactive amines but were not conducted by dietary modification in every day circumstances over several weeks.

Claims have been made for causal associations between food intolerance and an ever increasing number of diseases or exacerbation of diseases, but few of these have been substantiated by controlled trials. Because of the extensive publicity on food intolerances we believe that dietary manipulation may have a profound placebo effect, and consequently we performed a prospective controlled study of a diet low in vasoactive amines.

Patients and methods

All children included in the study were referred by their general practitioner or by another paediatrician to one or other of our children's outpatient clinics.

Migraine was defined as episodic headaches associated with nausea, vomiting, or visual disturbances when other diagnoses had been excluded. Patients with recurrent abdominal pain were not included unless they also suffered from migraine headaches. Children were excluded if they had previously tried dietary manipulations.

Two children had a history of epilepsy, three had asthma, and one had hay fever.

After medical consultation the dietitian obtained the dietary history and informed the parents of the nature of the trial. After enrolment the parents were given open access to the clinic to discuss any concern or difficulties. For the first eight weeks no dietary advice was offered and parents were asked to record all symptoms or signs in a standard diary given to

Table 1 *Foods excluded in diet B*

Foods containing vasoactive amines
Chocolate
Cheese
Yoghurt
Citrus fruits and citrus fruit juices, squashes, and cordials
Bananas, pineapple, raspberries, plums
Peas, broad beans, avocado pears
Yeast and meat extracts
Shellfish
Smoked, pickled fish
Game

Foods containing caffeine
Strong tea, strong coffee
All cola drinks unless free of caffeine

them. Children who had at least one migraine headache every two weeks were then randomly allocated to receive either a diet rich in fibre that did not exclude foods high in vasoactive amines (diet A) or the same high fibre diet that did exclude foods high in vasoactive amines (diet B) for an eight week period. The foods forbidden during this time are listed in Table 1. Parents were asked to continue recording symptoms during the trial period.

A crossover method was not used as it was thought that the patients who improved on one diet would be reluctant to switch to another and compliance might be lost

Eighty children were recruited to the initial assessment, of whom 61 were suitable for inclusion. Thirty nine of these children successfully completed the trial; the reasons for non-completion of the trial are summarised in Table 2. The child and parents were seen by the dietitian four weeks after starting the diet and again four weeks later, when the trial was concluded. No patients received prophylactic treatment with drugs during this period, though they were encouraged to use simple analgesia to relieve headaches. The diet was discussed fully with the family and no suggestion was made that one diet was likely to be more effective than another.

Initially, a simple scoring system was used to grade the severity of the headaches and accompanying symptoms. As this correlated strongly with the number of headaches the latter, being a less subjective variable, was used in the final analysis.

Table 2 *Reasons for excluding patients during study*

Forms missing	6
Failure to return	5
Modifying diet themselves	4
Drugs prescribed by general practitioner	3
Doubtful diagnosis	3
Appendicitis	1

Table 3 *Characteristics of the patients according to feeding regimen*

	Feeding regimen	
	Diet A	*Diet B*
Mean age (years)	10 33	11 08
Age range (years)	3 58–15 25	5 08–15 58
Sex (M F)	12 8	12 7
Family history of migraine	10	8
Duration of history of migraine (months)	3–96	1 5–120

Table 4 *% Improvement seen in patients with migraine given high fibre diet alone (diet A) or high fibre and low vasoactive amine diet (diet B)*

Feeding regimen							
Diet A				*Diet B*			
Case No	*No of attacks*		*% Improvement*	*Case No*	*No of attacks*		*% Improvement*
	Eight weeks' assessment	*Eight weeks' on diet*			*Eight weeks' assessment*	*Eight weeks on diet*	
1	27	0	100	1	6	0	100
2	6	1	80–89	2	9	0	
3	5	1		3	6	0	
4	14	3	70–79	4	33	6	80–89
5	4	1		5	17	3	
6	21	7	60–69	6	18	4	70–79
7	5	2		7	8	2	
8	10	4		8	8	3	60–69
9	43	17		9	35	16	50–59
10	7	3	50–59	10	12	6	
11	4	2		11	12	6	
12	6	3		12	6	4	30–39
13	15	9	40–49	13	13	9	
14	20	12		14	7	5	20–29
15	8	5	30–39	15	13	10	
16	17	11		16	15	12	
17	25	17		17	11	11	0
18	17	13	20–29	18	4	4	
19	8	14	Worse	19	30	42	Worse
20	5	14					
Total	267	139			263	143	

Results

Of the 39 children who completed the trial, 20 were assigned to diet A and 19 to diet B. The two groups were similar in age, sex, family history of migraine, and duration of history of migraine (Table 3). Before starting the study two children assigned to the high fibre diet (A) were thought by their parents to have attacks provoked by food: in one case cheese was the suspected agent and in the other tomatoes. Four of the children on the low amine diet (B) were similarly suspected to have attacks precipitated by food: in all cases these were foods high in vasoactive amines.

There was a significant reduction in the number of migraine headaches in both groups and there was no significant difference between the two groups. Patients assigned to the low amine diet (B) had a mean (SD) number of headaches of 13·84 (9·25) during the trial This dropped to 7·53 (9·41) during the time they were on their diet ($p<0\cdot01$). Sixteen of the 19 children had at least a 20% reduction in the number of attacks during this time and 10 of these had at least a 50% improvement. Patients assigned to a high fibre diet (A) had a reduction in the mean (SD) number of headaches from 13·35 (10·09) to 6·95 (5·84) during their time on the diet ($p<0\cdot01$). Eighteen of the 20 children in this group had at least a 20% reduction in the number of attacks and 11 of these had at least a 50% improvement (Table 4).

Discussion

Previous studies that have assessed the role of vasoactive amines in the aetiology of childhood migraine have produced conflicting results.[4] [5] As far as we are aware, this is the first published controlled study in children that compares a diet low in vasoactive amines with a control diet. Our findings show that removing vasoactive amines from the diet had no greater effect in reducing the number of migraine attacks than giving sensible advice about a high fibre intake in this group of children with uncomplicated migraine not selected for a history of food sensitivity. Due to the small number who completed the trial we cannot exclude the possibility that there are a small number of children who have a genuine biochemical idiosyncracy to vasoactive amines.

The great improvement we found in many of our patients remains unexplained In some it may have been due to reassurance to the parents and the child that the diagnosis was not more sinister. Many of the children were previously receiving a poor diet with irregular meals high in sugar and fat. Regular high fibre meals may have countered a tendency to hypoglycaemia,[8] but serial blood glucose measurements were not performed. It is possible that a high fibre intake protects against the absorption of dietary vasoactive amines, but we are not aware of any evidence to support this. In many the improvement was probably due to the placebo effect of prescribing changes to the diet.

Food allergy has recently been a focus of attention as an aetiological factor in childhood migraine. Studies of dietary manipulation without the use of control diets have reported improvement with the use of oligoantigenic diets. Egger *et al* reported a 93% relief of symptoms in a highly selected group of children with severe and complicated migraine treated with oligoantigenic diets.[6] Although no control diet was used, a proportion of children were challenged in a double blind fashion with antigens and controls. They concluded that most children with severe frequent migraine have food allergy. Monro *et al* drew similar conclusions about adults.[7]

In view of the findings of the present study we urge the use of a control diet in studies designed to show that exclusion of any dietary component or other dietary modifications improve disease, unless there is clear objective evidence that this is the case. as in conditions such as gluten enteropathy.

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Effect of spinal irradiation on growth

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SUMMARY Standing height, sitting height, and leg length were measured in 79 patients (aged 16–30 years), who had been given craniospinal irradiation (n=37) or cranial irradiation (n=42) in childhood for a brain tumour and had completed their growth. Their measurements were compared with established standards for sitting height and leg length in British children (aged 16–18 years). To examine the effects of spinal irradiation on spinal growth independent of growth hormone deficiency we analysed the leg length (LL) minus sitting height (SH) standard deviation score (SDS) and used the cranial group as controls. There was an overall significant difference between the median craniospinal LL–SH SDS (1·98) and the median cranial LL–SH SDS (0·545). Within the craniospinal group there was a significant correlation with age at treatment, but there was no such correlation for the cranial group. After splitting age at treatment into three groups (0<5, 5<10, and 10–15 years) there was a significant difference between the LL–SH SDS of the craniospinal and cranial groups for each of the age ranges.

In conclusion, spinal irradiation has a profound effect on spinal growth and the younger the child is when given irradiation the greater the subsequent skeletal disproportion. Our most conservative figures indicate that the eventual loss in height is 9 cm when irradiation is given at 1 year, 7 cm when given at 5 years, and 5·5 cm when given at 10 years.

Impaired growth leading to short stature may complicate the treatment of malignant disease. Radiation induced growth hormone (GH) deficiency and spinal irradiation are two major adverse factors that contribute to the short adult height achieved by many patients treated for brain tumours and acute lymphoblastic leukaemia in childhood. While radiation induced GH deficiency has been studied quite extensively,[1] the effect of irradiation of the spine on spinal growth has rarely been studied. Neuhauser *et al* suggested that the effects of irradiation on the vertebral bodies were dose and age related.[2] Probert *et al* concluded, however, that children receiving spinal irradiation under the age of 6 or at the time of puberty showed particularly pronounced retardation of spinal growth.[3]

In this study of children treated for brain tumours we have analysed the impact of age at spinal irradiation on final height achieved, and estimated the eventual loss in stature attributable to impaired spinal growth.

Patients and methods

Seventy nine patients (42 males and 37 females) previously treated for a brain tumour in childhood were studied. In all patients a surgical procedure consisting of either partial or complete removal of the primary tumour or biopsy alone was performed. After surgery 37 patients (23 males and 14 females) received craniospinal irradiation, while the remaining 42 (19 males and 23 females) received cranial irradiation alone.

In no child did the primary tumour directly involve the hypothalamic-pituitary axis. The histology of the primary tumour in the craniospinal group was medulloblastoma (26 cases), ependymoma (six), pineal tumour (three), and astrocytoma (two) and in the cranial group was glioma (37), ependymoma (two), angioma (two), and neuroma (one)

In the craniospinal group three radiation schedules had been used for the spinal irradiation. Fifteen children received kilovoltage irradiation with a total dose of 2700 cGy in 17 fractions over 22 days at posterior border or vertebral bodies: the remaining 22 patients received megavoltage irradiation with a total dose of either 3000 cGy (n=17) or 3500 cGy (n=5) in 20 fractions over 27 days to whole vertebra.

The age at which the children in the craniospinal group received irradiation ranged from 1 to 15 years and in the cranial group from 2 to 15 years Subsequently, eight of the children in the craniospinal group and six in the cranial group received treatment with GH for radiation induced GH deficiency.

At the time of the study all 79 patients had completed their growth. Their ages ranged from 16 to 30 years. No patient developed sex steroid deficiency that necessitated replacement therapy either as a consequence of radiation induced gonadotrophin deficiency (cranial irradiation) or from direct radiation induced gonadal damage (spinal irradiation). All had undergone puberty spontaneously Standing and sitting height measurements were performed using a Harpenden Stadiometer and sitting height table Subischial leg length was obtained by subtracting sitting height from standing height Standard deviation scores for sitting height and subischial leg length were calculated for chronological age using published tables,[4] with the exception of those aged over 18 years for whom the standard deviation score (SDS) was calculated as if for an 18 year old.

Statistical evaluation was performed using the Mann-Whitney U test, Kruskal-Wallis non-parametric analysis of variance (ANOVA), Spearman's correlation, and linear regression analysis where appropriate.

Results

The age at irradiation, standing height SDS, sitting height SDS, leg length SDS, and leg length-sitting height (LL–SH) SDS are shown in the Table. There was no significant difference in sex distribution, mean ages, or number of children treated with GH between the cranial and craniospinal groups.

There was a significant difference between the median standing height SDS of the two groups (−2·37 *v* −1·14; Mann-Whitney U test, p<0·0005) Within both the craniospinal group (Spearman's p=0·63, p<0·0001) and the cranial group (Spearman's p=0·45, p<0·005) there was a correlation between standing height SDS and age at irradiation

There was a significant difference between the median sitting height SDS of the two groups (−3·27 *v* −1·19; Mann-Whitney U test, p<0·0001). Within both the craniospinal group (Spearman's p=0·62, p<0·001) and the cranial group (Spearman's p=0·45, p<0·005) there was a correlation between sitting height SDS and age at irradiation.

There was no significant difference between the median leg length SDS of the two groups (−1·12 *v* −0·55; Mann-Whitney U test, p>0·1). Within both the craniospinal group (Spearman's p=0·46, p<0·005) and the cranial group (Spearman's p=0·35, p<0·05) there was a correlation between leg length SDS and age at irradiation

To concentrate on the impact of spinal irradiation rather than other adverse factors responsible for short stature the LL–SH SDS results were analysed in both groups and by splitting each group into three age divisions (0<5 years, 5–10 years, and 10–15 years) for cross comparison. There was a significant difference between the median LL–SH SDS of the two groups (1·98 *v* 0·55; Mann-Whitney U test, p<0·0001). These results were reinforced by the significant differences observed for each of the three age groups between the cranial and craniospinal groups. Interestingly, the median LL–SH SDS of the cranial group (0·55), as well as the median LL–SH SDS of the craniospinal group (1·98), was significantly different from normal. Within the craniospinal group there was a significant correlation with age at irradiation (Spearman's p=−0·4, p<0·02), which was maintained even if the eight children who received treatment with GH were excluded from analysis; no such correlation existed, however, within the cranial group (Figure).

To see if the three radiation schedules for spinal irradiation had different effects on spinal growth the median LL–SH SDS were compared between the three groups and no significant differences were found.

Finally, a quantitative estimate was made of the loss in eventual stature caused by irradiation of the spine at different ages. Using the linear regression equations shown in the Figure, the LL–SH SDS in both the craniospinal and cranial irradiation groups were calculated at 1, 5, and 10 years of age. In each case, subtracting the LL–SH SDS result for the cranial group from that obtained in the craniospinal group provided the LL–SH SDS difference caused

Table *Age at irradiation (months) and standing height, sitting height, leg length, and leg length—sitting height standard deviation scores (SDS) in 79 patients treated with cranial or craniospinal irradiation*

Treatment group	*Mean (SD) age at irradiation*	*Median (range) SDS*			
		Standing height	*Sitting height*	*Leg length*	*Leg length-sitting height*
Cranial (n=42)	100 (48)	−1·14 (−2·83 to +0·80)	−1·19 (−5·16 to +1·45)	−0·55 (−4·87 to +1·29)	0·55 (−1·52 to +2·96)
Craniospinal (n=37)	107 (49)	−2·37 (−4·87 to +0·41)	−3·27 (−6·13 to +0·52)	−1·12 (−3·07 to +2·71)	1·98 (−0·45 to +5·35)

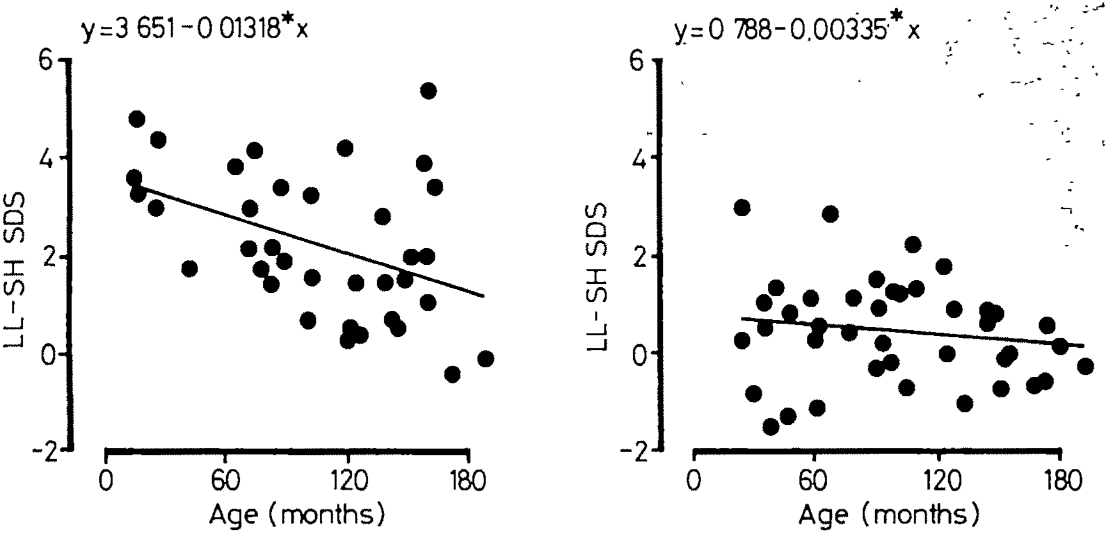

Figure *Leg length–sitting height standard deviation score (LL–SH SDS) versus age at which irradiation was given for the craniospinal (left) and cranial (right) groups. The linear regression equation is stated for both groups (y=LL–SH SDS and x=age in months)*

by spinal irradiation. The differences in LL–SH SDS were 2·745, 2·273, and 1·683 for 1, 5, and 10 years, respectively. If it was assumed that these differences were totally attributable to impaired spinal growth due to spinal irradiation then 'translating' the SDS differences into centimetres of 'lost spinal height' on the standard chart[4] indicated that the eventual loss in height was 9 cm if irradiation was given at 1 year, 7 cm if given at 5 years, and 5·5 centimetres if given at 10 years.

Discussion

The results of this present study confirm that adults previously treated for a brain tumour were short.[5] Short stature occurred in those previously treated with cranial irradiation (median standing height SDS −1·14) but was more pronounced in those who received craniospinal irradiation (median standing height SDS −2·37) Two major factors contributing to growth failure were radiation induced GH deficiency and spinal irradiation. The correlation between either standing height SDS or sitting height SDS and age at irradiation reflects the fact that the younger the age at which GH deficiency or other adverse factors affecting growth occur then the greater the loss in growth potential Both standing height and sitting height SDS correlations with age at treatment were greater for those children receiving craniospinal rather than cranial irradiation, due to greater impairment in spinal growth seen in younger children.

The conclusion that spinal irradiation was a significant adverse factor in the growth of these children was further supported by the observation that there was no significant difference between the median leg length SDS of the craniospinal and cranial groups.

To disentangle the effects of GH deficiency and spinal irradiation on spinal growth we analysed the LL–SH SDS in both groups. This was necessary for two reasons; firstly, the GH state of many of these patients (25%) had not been formally assessed and, secondly, GH deficiency does lead to a short spine but does not cause skeletal disproportion. The LL–SH SDS therefore provided an estimate of the height loss due to spinal irradiation, which could not be calculated with the spinal height SDS data alone.

It was of interest to note that the median LL–SH SDS of the cranial group (0·545) was significantly different from normal (0) This probably reflected the use of the Harpenden Stadiometer for making our measurements, which was not the method used in the construction of the original SDS, which were formulated using an anthropometer;[4] it may have been that this overestimated the sitting height of the children studied. In our calculations, therefore, the cranial group provide a very important body of control data not otherwise available

Our results in the very young child confirmed the earlier observations of Probert *et al* that spinal growth was considerably impaired if the spine had been irradiated before 6 years of age.[3] We disagreed with these authors, however, over their conclusion that irradiation of the spine during puberty was particularly likely to impair spinal growth.[3] The younger the child at irradiation the greater the loss in growth potential, from 9 cm at 1 year to 5·5 cm at 10 years.

Medulloblastoma and ependymoma exfoliate cells into the cerebrospinal fluid, and seeding may occur most commonly in the spinal canal. Spinal irradiation is given to prevent spinal relapse of disease. It can be seen, however, that the price for such protection is high in terms of loss of growth potential. It may be that the same spinal protection' can be afforded by a lower dose of spinal irradiation. Such studies need to be undertaken in the future.

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Decreasing incidence of coeliac disease

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SUMMARY Between 1960 and 1974 the incidence of coeliac disease in children under 12 years in County Galway remained fairly constant, but since 1975 it has fallen by 62% and the lowered incidence seems well established. The number of those who were breast fed and the age at which first gluten feeding took place during the 22 years both increased significantly and from the mid-70s total protein content and osmolarity of proprietary cow's milk formulas were reduced. All three factors may be relevant. A negative correlation with the incidence of gastroenteritis was found.

Reports from other centres[1-3] and our experience[4] led us to review the incidence of coeliac disease in County Galway over a 22 year period The incidence of the first 11 years of this period, which we reported in 1973,[5] was then the highest known This area has the highest recorded prevalence of human leucocyte antigens (HLA) B8 and DR3,[6] and this county has favourable features for a study of this kind as the population has remained fairly stable.

Until 1979 ours was the only centre in County Galway that performed intestinal biopsy examinations (since then we have been informed of cases diagnosed in children in another hospital undertaking such examinations). These factors, together with the presence of departments with a specific interest in the disease, have probably resulted in our area having as high an ascertainment as any other area where incidence has been studied.

Patients and methods

Intestinal biopsy specimens were taken with Crosby or Watson capsules from the distal duodenum or proximal jejunum under fluoroscopic control. All appraisals of dissecting microscope and histological features in children were made by the same person (BM) throughout the study and classified as described previously [7] All biopsy specimens were classified as grade II or III Under the dissecting microscope the mucosa was either flat or convoluted, histological section showed either absence of villi or low villous projections, with elongation of crypts, reduction in height of enterocytes, increased ratio of lymphocytes to enterocytes in the epithelium, and increased cellularity in the lamina propria, consisting mainly of plasma cells.

One hundred and three children under 12 years were diagnosed during 22 years, 54 of whom were the subject of our previous study.[5] The rate of incidence for each period of 11 years was struck two years after the end of that period to make them comparable. For example, only children born between January 1960 and the end of December 1970, who had presented with coeliac disease before the end of 1972, were included in that period. In Table 1 the 22 years have been divided into four equal periods. Gluten challenge to confirm the diagnosis by inducing mucosal relapse was carried out in 13 children, all of whom relapsed and who form part of a separate report.[8] In 18 children the persistence of gluten intolerance was shown by incomplete mucosal recovery due to poor compliance with the diet. Gluten challenge was not carried out on the remainder as we found that mucosal relapse occurred in 47 of 50 children given gluten challenges, having excluded those with acute enteritis, cow's milk intolerance, and immune deficiency (other than selective IgA deficiency) [8]

A comparison was made between the annual admission to our centre of children under 12 with gastroenteritis during the 22 years and cases with coeliac disease presenting in the same years (irrespective of their birth years). This is the only centre in the county with a designated gastroenteritis and isolation unit, and we used admissions rather than notification of gastroenteritis as the latter refers only to specific bacterial pathogens and is incomplete

Results

Table 1 shows total births for County Galway and cases of coeliac disease according to their year of birth and expressed as a ratio of total births and per

Table 1 *Total births and No of cases of coeliac disease according to their year of birth as ratio of total births and per 1000 births in County Galway over a 22 year period (1960–81), divided into 5·5 year quarters*

	Period of birth			
	1 Jan 1960–30 June 1965	*1 July 1965–31 Dec 1970*	*1 Jan 1971–30 June 1976*	*1 July 1976–31 Dec 1981*
Total births	16313	15874	18005	19271
Cases of coeliac disease				
As ratio of total births	1:604	1:590	1:514	1:1376
Per 1000 live births	1·65	1·69	1·94	0·73

1000 births, in four successive periods of 5·5 years. The incidence of coeliac disease for the first three periods was similar but fell by 62% during the last quarter. The fall began in 1975 and contrasted with a rise in birth rate, which was slightly in excess of the rate of growth of the population.* These figures also contrasted with those for the prevalence of adult coeliac disease,* which have continued to rise since the setting up of a department of gastroenterology in 1965. Admissions for gastroenteritis rose slightly during the fourth period of study, whereas cases of childhood coeliac disease decreased.*

Changes in infant feeding practices. Before the mid-70s, most artificially fed Irish infants received formulas based on largely unmodified cow's milk, and some were still receiving foods based on liquid cow's milk; relatively few were receiving formulas based on 'humanised' cow's milk. By 1978,[9] all infant formulas were modified in a similar manner, the major changes being a reduction in total protein and electrolyte content to concentrations similar to those in breast milk. There was also a trend to replace a major proportion of butterfat by vegetable fats. These changes were concurrent with those in the United Kingdom. Even though some formulas used high proportions of whey protein and thus of β-lactoglobulin compared with casein and were potentially more antigenic it is thought that processing reduces antigenicity,[11] so that from the mid-70s Irish babies received feeds that were probably less antigenic than hitherto and that were closer in osmolarity to breast milk, as well as having less butterfat.

No national or county records for breast and gluten feeding are available for the earlier part of the period under review, so one of us (BM) reviewed some thousands of personal records of patients, referred in this area, extracting from them all those that had valid information concerning breast and gluten feeding.

Table 2 shows that there were significant increases in those breast feeding for more than a month (from 12% to 28%) and in the mean age of gluten introduction (from 2·3 to 4·2 months) in the first compared with the fourth 5·5 year period. Mothers breast fed for somewhat longer in the last quarter (3·1 months) compared with the first (2·6 months). The social groups in this review had a bias towards the more affluent and therefore probably towards a greater tendency to breast feed and to be more conservative about the introduction of gluten, but they were similar in both periods. We believe that these figures were representative of a fairly broad range of the county's predominantly rural population. A survey of feeding practices in this area in February and March 1986 by area medical officers at our request confirmed the trends in the personal review, in that 34·5% of 665 infants of all social groups seen at 7 months for developmental screening were breast fed for more than one month, and the mean age of gluten introduction in 670 infants was 3·8 months.

As far as the relation of breast and gluten feeding to the incidence of coeliac disease was concerned, we sought information from a continuing study of a cohort of 52 patients from 1960 to 1970 in whom coeliac disease was confirmed by gluten challenge; we were able to find some controls comparable in age and sex from hospital records of the same period. Four of 20 children with coeliac disease were breast fed for over a month compared with nine of

Table 2 *Personal records of breast and gluten feeding for the first and last 5·5 year periods*

	Breast feeding for over one month (%)	*Mean age at which gluten started (months)*
1 Jan 1960–30 June 1965	12·0 (n=319)	2·3 (n=130)
1 July 1976–31 Dec 1981	24·0* (n=163)	4·2* (n=45)

*Both significant, $p<0.001$
n=No of infant records

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*Data available on request

40 controls. Fifteen (63%) of 24 children with coeliac disease were first fed gluten before 2 months compared with 20 (54%) of 37 controls. The differences were not significant

Discussion

During the period under review, as there has been little change in the genetic background in County Galway, with its high prevalence of HLA-B8 and HLA-D3, we believe that the declining incidence of childhood coeliac disease must be due to environmental factors. As there was a negative correlation with gastroenteritis during the last quarter when incidence of coeliac disease decreased we assume that changes in infant feeding were the major causes of the decreased incidence

A retrospective study in three Italian cities argued that in families with a child who had coeliac disease siblings who were artificially fed were four times more likely to have the disease than those who were breast fed for more than a month.[11] Our smaller retrospective analysis did not show a similar trend. We have shown that breast feeding was over twice as prevalent in the last compared with the first quarter of the 22 years of study and that the mean time of gluten introduction was almost doubled. In addition, infant formulas were modified for almost all of the last quarter.

As the newborn infant matures his immunological efficiency improves: the gut becomes less permeable to macromolecules[12] and there is an increase in both the number of IgA plasma cells in the lamina propria and the quantity of secretory IgA in the glycocalyx and lumen.[13 14] Breast feeding provides an optimal nutritional and immunological state in the gut, providing intraluminal IgA as well as other anti-bacterial and trophic factors.[15]

A role for IgA in the prevention of coeliac disease is supported by our finding of selective IgA deficiency in 11 of 354 patients with the disease; this represents a 15-fold increase in the incidence of coeliac disease in these patients compared with that in the general population.[16] The increased concentrations of IgA expected in the gut with increasing age[14] may render it less susceptible to a pathological reaction to gluten even at 4 as opposed to 2 months. The high concentrations of proteins and solutes in the previously unmodified cow's milk formulas may have increased the susceptibility of the gut to abnormal interaction with gluten. We cannot identify any one factor responsible for the decreasing incidence of coeliac disease but believe that major factors have been the increase in both the number of mothers who breast fed and the age of first gluten feeding together with the lowered antigenicity and osmolarity of infant formulas.

We have no evidence based on intestinal biopsy examination for the incidence of coeliac disease in the county before 1960. In the earlier years of the century breast feeding would probably have been more prevalent and wheat feeding introduced at a later stage. If this were the case the incidence of coeliac disease may have been such that the high incidences from 1960 to 1976 represented a response to the prevailing fashion of more artificial feeding including early wheat feeding, and the present lower incidence represents a return to a basic level. We have no evidence so far that the decreased incidence reflects merely a postponement of the expression of the disease as we have not yet seen further cases of coeliac disease born between 1976 and 1981.

Since our original report of a high incidence,[5] additional cases of coeliac disease have been identified in the cohort born between 1960 and 1971, causing a rise in incidence from 1/597 to 1/450. In that publication we estimated that the incidence of the disease in the total population of County Galway may have been as high as 1/300, that figure being derived from the incidence in children and the mean annual rate of detection in adults, neither symptomatic nor diagnosed in childhood. By the time this cohort reaches old age an incidence of 1/300 may have become fact rather than speculation.

We acknowledge the help of our colleagues, medical and nursing, Dr Kevin Connolly for details of children diagnosed in Portiuncula Hospital, Ballinasloe, A E Mettler of Farley Health Products Ltd for information on cow's milk formulas, officials of the Central Statistics Office, Dr E McHale for coordinating the survey of infant feeding by area medical officers, and Dr J Colaco for help with statistics The studies were aided by the Western Health Board, the Medical Research Council of Ireland, and the Wellcome Trust

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Humoral response to α gliadin as serological screening test for coeliac disease

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SUMMARY The diagnostic value of measuring α gliadin antibodies in children with suspected coeliac disease has been evaluated prospectively. Jejunal biopsy and α gliadin antibody measurements were performed in 77 consecutive children who were being investigated for a suspected malabsorption syndrome. The typical small intestinal histological lesion of coeliac disease was found, and this diagnosis was subsequently confirmed clinically in 20 children. Raised IgG α gliadin antibody concentrations were found in 19 (95%). Fifty of 57 patients (88%) with a normal jejunal mucosa had normal α gliadin antibody concentrations. These results are similar to those previously reported in a prospective study of adult patients with coeliac disease and indicate that measurement of α gliadin antibody is a highly sensitive and specific screening test for childhood coeliac disease.

The gluten sensitive enteropathy characteristic of coeliac disease is thought to be caused by an abnormal immunological reaction to wheat protein.[1] Previous studies in adult patients with coeliac disease have shown both cellular[2 3] and humoral[4] sensitisation to α gliadin, a purified fraction of wheat protein. In a prospective study of 90 adult patients α gliadin antibody concentrations were raised in 82% of 44 patients with untreated coeliac disease, whereas normal antibody concentrations were found in 87% of 46 patients with normal jejunal mucosa.[4] This study has now been extended to include a total of 206 patients and measurement of α gliadin antibody has continued to show a specificity of 88% and sensitivity of 81%. The present study assessed the value of α gliadin antibody measurement in the diagnosis in children.

Patients and methods

Prospective study: patients and controls. Children who presented with symptoms suggestive of a malabsorptive disease were assessed. A consecutive group of 77 children undergoing a jejunal biopsy examination were studied without knowledge of their clinical or histological state. Their ages ranged from 9 months to 15 years, with a median value of 6 years. IgG α gliadin antibody concentrations were measured and correlated with their jejunal histology. Twenty children had coeliac disease diagnosed on the basis of their jejunal histology and clinical symptoms while on a normal diet, and all 20 responded clinically to a gluten free diet. At diagnosis, 16 biopsy specimens had subtotal villous atrophy, and the remaining four had partial villous atrophy. Ten of these children were subsequently re-exposed to gluten; clinical deterioration accompanied this challenge and the biopsy specimens again showed changes consistent with coeliac disease. The remaining 57 children had a normal small intestinal mucosa.

IgA α gliadin antibody concentrations were measured in 12 of the 20 patients, and both IgG and IgA antibody concentrations to soya protein extract and β lactoglobulin were also measured in 12 children with confirmed coeliac disease and in 31 children with normal jejunal biopsy specimens.

Establishment of IgG and IgA α gliadin antibody concentrations in normal children. Serum samples were obtained from 54 control children, whose ages ranged from 1 to 15 years, with a median age of 7 years. These children had been admitted to hospital for non-gastrointestinal disorders and were assessed for specific IgG α gliadin antibody concentrations, which were correlated with their age. IgA α gliadin antibody concentrations were also assessed in 45 of these subjects.

Serum α gliadin antibody detection. Serum antibody concentrations were measured by enzyme linked immunosorbent assay (ELISA) as previously described.[4] The results are expressed as ELISA indices (EI), where

$$\text{EI} = \frac{\text{Mean of three originally derived readings of the test sample}}{\text{Mean of three originally derived readings of the background}}$$

Antigens. α gliadin was prepared from gliadin by ion exchange chromatography on a carboxymethylcellulose column as described by Gehrke *et al*[5] Soya protein extract was prepared by 70% ethanol extraction from soya flour, as described for the preparation of alcohol soluble gliadin proteins from crude gliadin.[6] β Lactoglobulin was obtained from Sigma.

Statistics. The data were analysed by the Wilcoxon rank sum test.

Results

α Gliadin antibody concentrations in normal control children. The IgG and IgA α gliadin antibody concentrations found in the control children are shown in Figure 1. The concentrations gradually increased with age and reached adult values at about 12 and 7 years of age, respectively The increase was more pronounced in the IgG class α gliadin antibody.

Prospective analysis of α gliadin antibodies in children presenting with a possible malabsorptive disease. In 77 children who underwent jejunal biopsy examination coeliac disease was diagnosed in 20, 19 of whom had raised concentrations of IgG α gliadin antibody (sensitivity 95%) (Fig. 2, Table). The remaining 57 children had a histologically normal small intestinal mucosa, of these, 50 had normal α gliadin antibody concentrations (specificity 88%). IgA α gliadin antibody concentrations were also estimated in 12 of the 20 children with coeliac disease (Fig. 3) In the untreated group with coeliac disease, although the mean (SD) concentration (2·09 (1·35)) was significantly raised over the mean (SD) of the control group (1·28 (0·50)) ($p<0·05$), only five of the 12 patients tested fell above the normal range.

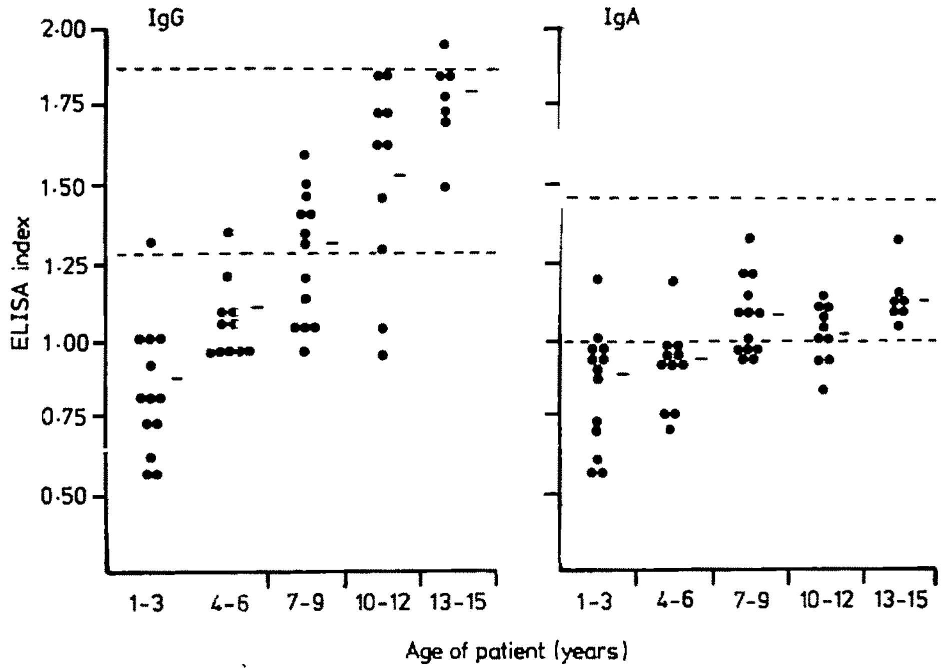

Fig 1 *Variation in IgG and IgA α gliadin antibody concentrations with age in the normal population. Results expressed as mean (SE) enzyme linked immunosorbent assay (ELISA) index The solid black lines indicate the mean (SD) normal adult value.*

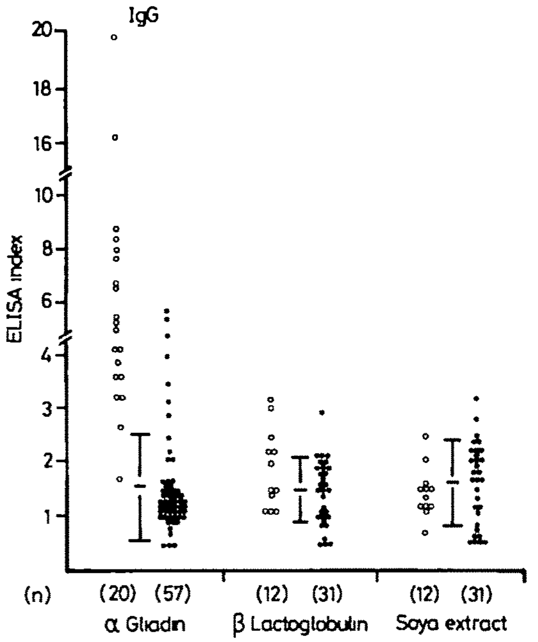

Fig. 2 *IgG antibody concentrations to α gliadin, β lactoglobulin, and soya protein extract in untreated patients with coeliac disease (○) and control subjects (●) The bars indicate the mean (SD) enzyme linked immunosorbent assay (ELISA) index of the control group*

Table *Correlation between IgG α gliadin antibody results and mucosal histology in 77 children*

	Biopsy result	
	Positive	*Negative*
α Gliadin antibody result		
Positive	19	7
Negative	1	50
Total	20	57

Sensitivity (probability of detecting coeliac disease when the test result is positive)=95%, specificity (probability of excluding the disease when the result is negative)=87·7%

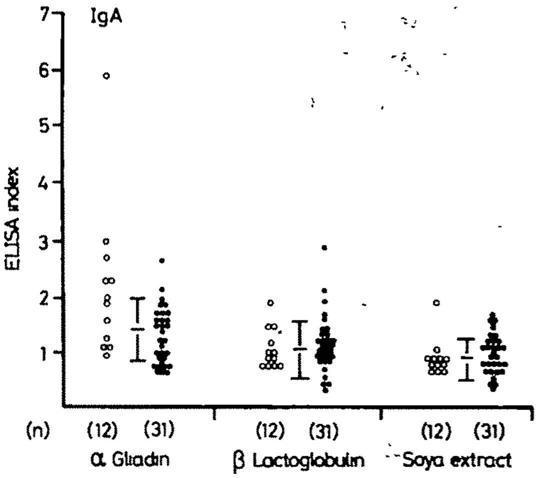

Fig. 3 *IgA antibody concentrations to α gliadin, β lactoglobulin, and soya protein extract in untreated patients with coeliac disease (○) and control subjects (●). The bars indicate the mean (SD) enzyme linked immunosorbent assay (ELISA) index of the control group.*

Incidence of antibodies to other dietary antigens in children with coeliac disease and normal children. The results for IgG and IgA concentrations to soya protein extract and β lactoglobulin in 12 children with coeliac disease proved by biopsy examination and 31 controls are shown in Figures 2 and 3, respectively; the α gliadin results are included for comparison. Using β lactoglobulin, the mean (SD) IgG antibody concentration (1·98 (0·70)) of the untreated group with coeliac disease was raised above the mean (SD) of the control subjects (1·507 (0·593)). The difference between the two groups was not significant, however, and although four of the patients with coeliac disease had raised titres, four of the controls who were being investigated for gastrointestinal symptoms also had raised antibody concentrations. No difference was seen between the IgG concentrations to soya protein extract in either the group with coeliac disease or the control group.

Detection of specific IgA antibodies to β lactoglobulin and soya protein antigens showed no difference in the response of the untreated children with coeliac disease and the controls.

Discussion

This prospective study shows the diagnostic value of measuring α gliadin antibody in children with symptoms of malabsorption and in whom coeliac disease is suspected. When 77 consecutive children were investigated 20 had the typical small intestinal histological lesion of coeliac disease, 19 of whom had raised IgG α gliadin antibody concentrations, whereas 50 of the 57 children with normal small intestinal histology had normal antibody concentrations. All of the 20 children with the coeliac lesion showed improvement clinically on gluten free diet, and the 10 children who were subsequently challenged with gluten showed a clinical relapse, which was histologically confirmed on further biopsy examination. This gave the test a sensitivity of 95% and specificity of 88%, and these values agree well with our previous prospective study of adults with suspected coeliac disease.[4] The results also confirm the findings of Burgin-Wolff *et al*, who described the only other study in which measurement of wheat protein antibodies was prospectively evaluated as a screening test in childhood coeliac disease.[7] They employed gliadin as antigen in a fluorescence assay system and found raised antibody concentrations in all their patients with coeliac disease and in 16% of those without coeliac disease. The two studies further concur in that measurement of IgG class antibodies was most informative and that antibody concentrations to other dietary antigens were of no diagnostic help.

In previous non-prospective studies of coeliac disease an increased incidence of IgG antibodies to wheat protein antigens was shown[8-11] As wheat protein antibodies were also found in other diseases, however, these assays could not be relied on to discriminate consistently between patients with coeliac disease and those without. Consequently, many investigators have recommended the measurement of IgA wheat protein antibodies[10-13] Although the finding of wheat protein antibodies of IgA class is generally quite specific for the diagnosis of coeliac disease, several reports show this to be an insensitive test, especially in older children and adults.[10 11 13] In this study, although IgA α gliadin antibodies were found in fewer of the patients without coeliac disease, raised concentrations were detected in only five of the 12 serum samples of patients with coeliac disease, rendering the detection of IgA α gliadin antibodies unsuitable as a screening test.

The antigen used in our assay was α gliadin. There is evidence that the major cellular and humoral immune response in patients with coeliac disease is directed towards this particular subfraction of gliadin[3 14 15] and that it is more toxic to coeliac jejunal tissue than other wheat protein fractions.[16-18] Unfractionated gliadin used in this ELISA system did not discriminate adequately between patients with and without coeliac disease[4] As unfractionated gliadin was used in previous studies this may explain the difficulties experienced in differentiating the patient group from the control group,[8 13] although in some assays gliadin can be a satisfactory test antigen.[7]

To determine the effect of age on α gliadin antibody responses, samples from normal control children aged 1 to 15 years were evaluated A gradual increase in both IgG and IgA α gliadin antibody concentrations was found that paralleled the age related increase in total immunoglobulin concentrations The use of age matched controls was not necessary when screening for coeliac disease, however, as the titres obtained from the children with coeliac disease exceeded even the normal adult values. Raised antibody concentrations were found in seven of the control subjects. Of these, one patient had cystic fibrosis, two had a strong family history of coeliac disease, one had cow's milk protein intolerance, one was less than the 25th weight and 50th height centiles and had diarrhoea, and the remaining two had persistent diarrhoea It has been documented that patients with coeliac disease vary in their sensitivity to gluten and may require a high gluten intake for several months before showing histological changes.[19] Gluten challenge might therefore induce the characteristic lesion of coeliac disease in some of this group with raised α gliadin antibody concentrations.

Screening tests for coeliac disease, including measurement of faecal fat, measurement of D-xylose absorption, radiological examination of the small bowel, haematological investigations, and detection of reticulin antibodies have been used in the past. None of these investigations is regarded as adequately sensitive or specific for coeliac disease.[20-22] In contrast, our study shows that as only one patient with true coeliac disease had normal antibody concentrations measurement of α gliadin antibody using ELISA in children with suspected coeliac disease is a highly sensitive test. As this test is simple and cheap to perform it is useful for screening patients before performing the ultimate investigation—that is, small intestinal biopsy. The assay may also help to distinguish patients likely to respond to gluten withdrawal from those with other malabsorptive diseases. Finally, as gluten withdrawal is accompanied by a fall in antibody concentrations[4 7] α gliadin antibody measurement may be used to monitor dietary compliance.

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Serum 1,25 dihydroxyvitamin D and osteocalcin concentrations in thalassaemia major

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SUMMARY In view of the claim that low 25-hydroxyvitamin D (25-OHD) concentrations may contribute to the pathogenesis of bone disease in patients with β thalassaemia major and iron overload, we have assessed the concentrations of 25-OHD, 1α,25 dihydroxyvitamin D (1α,25$(OH)_2$D), parathyroid hormone, and osteocalcin in such patients. 25-OHD concentrations were significantly lower in patients with thalassaemia major and iron overload than in controls and in some patients were subnormal or undetectable. 1α,25$(OH)_2$D concentrations were, however, normal in all patients and were similar to those in controls. Serum parathyroid hormone and plasma calcium concentrations were also normal and not significantly different from those in controls Although 25-OHD concentrations increased significantly between January and June, there was no change in 1α,25$(OH)_2$D concentrations. 25-OHD concentrations remained lower than control values, even in June. Parathyroid hormone concentrations fell, but not significantly, between January and June, but calcium concentrations did not alter. Osteocalcin concentrations were normal in all patients except one, who had extremely low concentrations of this protein The concentration of osteocalcin was not related to 25-OHD or 1α,25$(OH)_2$D concentrations. Thus normal calcium homeostasis is maintained in patients with thalassaemia major despite low or low-normal 25-OHD concentrations; this is probably achieved through the maintenance of normal 1α,25$(OH)_2$D concentrations, which were indistinguishable from those in controls. Normal 1α,25$(OH)_2$D, parathyroid hormone, and osteocalcin concentrations argue against an important role for vitamin D deficiency in the pathogenesis of thalassaemic bone disease.

Previous studies on the vitamin D state of patients with β thalassaemia major and iron overload have shown that although these patients have no abnormalities in their plasma calcium and phosphate concentrations, the concentrations of 25-hydroxyvitamin D (25-OHD) are often low and are subject to seasonal variations.[1 2] It has been suggested by some authors that this marginal deficiency of 25-OHD may contribute to bone disease in patients with β thalassaemia major and iron overload[3] Bone disease in this condition may be severe enough to cause pathological fractures.[3] It is surprising therefore that no study investigating concentrations of 1α,25 dihydroxyvitamin D (1α.25$(OH)_2$D) has hitherto been published This is particularly important as parathyroid hormone deficiency is also known to occur in patients with β thalassaemia major and severe iron overload,[4] and parathyroid hormone regulates the renal hydroxylation of 25-OHD to 1α,25$(OH)_2$D. We therefore undertook a study to determine (1) whether 1α,25$(OH)_2$D concentrations were responsible for the normal and relatively constant calcium concentrations in these patients and (2) whether 1α,25$(OH)_2$D concentrations altered in these patients with the change in seasons We also undertook measurements of serum osteocalcin, an index of osteoblastic activity, in these patients

Patients and methods

A series of 15 patients (seven male and eight female, age range 18–28 years) with thalassaemia major were investigated. All patients had severe iron overload. Serum ferritin concentration ranged between 900 and 932 μg/l The patients had been treated with chelation therapy with subcutaneous desferrioxamine infusions. They were all fairly well, mobile, and active and were having blood transfusions at four weekly intervals. Aspartate transaminase activities ranged between 45 and 225 U/l (normal range 5–35 U/l). All patients had blood samples collected in January, and seven of them were reinvestigated in June of the same year.

Plasma calcium, phosphate, and albumin concentrations and alkaline phosphatase activity were measured using a SMAC Technicon Autoanalyser. Serum parathyroid hormone concentration was measured by a radioimmunoassay using an antibody directed against the mid-fragment of the parathyroid hormone molecule.[4] Serum 25-OHD concentration was measured by a technique modified from Preece *et al*[5] and serum 1α,25(OH)$_2$D concentration by the technique of Reinhardt *et al*[6] Osteocalcin in serum was measured by a specific radioimmunoassay as described by Deftos *et al* [7] (The reagents for these assays (parathyroid hormone, 1α,25(OH)$_2$D, and osteocalcin) were obtained from Immunonuclear Corporation, Stillwater, Minnesota, United States.) The details of the sensitivity and precision of these assays have been published before.[8]

Statistical analysis was carried out using Student's *t* test

Results

Calcium, phosphate, and albumin concentrations were within the normal range in all patients and were not different from those in controls (Table 1).

Serum 25-OHD concentrations of the 15 patients studied in January (mean(SD)· 12·6(6·7)nmol/l) were significantly lower than control values (mean(SD) 35(10)nmol/l) (Table 2). Ten of 18 patients studied in January had subnormal 25-OHD concentrations. The serum 25-OHD concentration was greater in June than in January in each of the seven patients in whom such paired samples were available. There were no corresponding increases in calcium concentrations (Table 1). The concentration of 25-OHD in these patients was also lower than that in controls during the summer, but this difference was not significant.

1α,25(OH)$_2$D concentrations were in the middle of the normal range of all patients, irrespective of concomitant subnormal or low-normal 25-OHD concentrations. There was no significant change in 1α,25(OH)$_2$D concentrations between January and June (Table 2).

Parathyroid hormone concentrations were within the normal range in all patients; they fell by a small but not significant amount between January and June (Table 2). A similar small diminution in parathyroid hormone was also observed in the controls. Parathyroid hormone concentrations in patients with thalassaemia were lower than those in controls in both summer and winter, but this difference was not significant.

Osteocalcin concentrations ranged between 0·3 and 11·7 ng/ml (mean(SD) 5·3(2·2)ng/ml); in one patient it was subnormal (0·3 ng/ml). Osteocalcin concentrations were not related to 25-OHD, 1α,25(OH)$_2$D, or parathyroid hormone concentrations.

Table 1 *Calcium and phosphate concentrations and alkaline phosphatase activity in patients with thalassaemia major and controls. Values are mean (SD) [range]*

	Calcium (nmol/l)	*Phosphate (nmol/l)*	*Alkaline phosphatase (IU/l)*
Patients with thalassaemia (winter)	2·43 (0·12) [2·25–2·55]	1·0 (0·12) [0·9–1·15]	105 (15) [86–130]
Controls	2·41 (0·13) [2·21–2·56]	1·1 (0·15) [0·85–1·18]	101 (16) [83–125]

Table 2 *Serum 25-hydroxyvitamin D (25–OHD) 1α,25 dihydroxyvitamin D (1α,25(OH)$_2$D), and parathyroid hormone concentrations in patients with thalassaemia and controls: effect of seasons. Values are mean (SD)*

	25-OHD (nmol/l)	*1α,25(OH)$_2$D (pmol/l)*	*Parathyroid hormone (pmol/l)*
Patients with thalassaemia			
Summer (n=7)	28 (12·1)**	86·1 (10·9)	36·4 (9·1)
Winter (n=15)	12·6 (6·7)*	88·9 (11·1)	40 (19)
Controls			
Winter	35 (10)	85 (20)	55 (15)
Summer	40 (12)	81 (19)	48 (16)

*$p<0·002$ when compared with controls in winter and $p<0·01$ themselves in summer
**$p<0·05$ when compared with controls in summer

Discussion

These data show that although serum 25-OHD concentrations are low-normal or subnormal in patients with β thalassaemia major, their serum 1α,25(OH)$_2$D concentrations are in the middle of the normal range. Furthermore, while pronounced seasonal variations of 25-OHD, concentrations occur, there is no seasonal alteration in 1α,25(OH)$_2$D concentrations. Plasma calcium concentrations also remained essentially unaltered. This is consistent with the fact that serum parathyroid hormone concentrations were within the normal range and did not alter significantly in these patients between January and June. It is noteworthy that significant vitamin D deficiency is associated with a rise in parathyroid hormone concentrations. We have previously shown this among Asians in the United Kingdom[9] and in the elderly.[8]

These data indicate that calcium homeostasis is normal in patients with thalassaemia major, although the relative lack of sunshine in the UK contributes to diminished vitamin D stores as reflected by low or low-normal 25-OHD concentrations. The deficiency is more pronounced in winter. There is, however, sufficient 25-OHD to provide an adequate substrate for 1α-hydroxylation by the kidney, and therefore these patients have normal concentrations of 1α,25(OH)$_2$D, even during the winter months. It is relevant to mention that administration of vitamin D to patients with osteomalacia who have low 25-OHD and 1α,25(OH)$_2$D concentrations can restore 1α,25(OH)$_2$D concentrations to normal very rapidly[10] and that minute quantities of calciferol are sufficient to generate large quantities of 1α,25(OH)$_2$D. 25-OHD concentrations in serum are expressed in nmol/l, while those of 1α,25(OH)$_2$D are expressed in pmol/l.

Serum osteocalcin concentrations are thought to be markers for osteoblastic activity.[11 12] As osteocalcin concentrations were normal in all patients except one it would seem that osteocalcin is not altered in most of these patients. This does not rule out the possibility, however, that the ratio of carboxylated to non-carboxylated osteocalcin may be altered in such patients. We have recently shown that carboxylation of osteocalcin in man is a vitamin K dependent process[13] and that it may be altered in patients with primary biliary cirrhosis.[14]

Thus these data suggest that vitamin D deficiency probably does not contribute to the skeletal abnormalities observed in most patients with thalassaemia major. These abnormalities are probably due to the pronounced and diffuse extramedullary haemopoiesis and possibly the deposition of iron in skeletal tissue known to occur in this condition.[15] Whether the deposition of iron actively interferes with ossification is not known. Bone biopsy examinations have shown evidence of abnormal bone formation, but osteomalacia is extremely rare.[15] There are reports, however, of the presence of thickened osteoid seams, without a lining of osteoblasts on these seams, in patients with β thalassaemia with severe untreated anaemia.[16] This occurrence was associated with normal serum 25-OHD concentrations. In contrast, in a rare case of β thalassaemia without anaemia a high turnover of bone was observed with normal osteoblasts around osteoid seams.[17] Thus anaemia itself may induce changes in the bone. Longstanding thalassaemia is associated with osteopenia and pathological fractures[3]—this could reflect cumulative effects of defective bone formation through various mechanisms

Another factor contributing to osteopenia and pathological fractures in this condition could be the delay in the onset, or total absence of puberty. Hypo-oestrogenism associated with amenorrhoea and delayed puberty have recently been incriminated in the pathogenesis of osteopenia in anorexia nervosa,[18] in women athletes,[19] and in ballet dancers.[20] Finally, treatment of anaemia per se has been shown to correct histological abnormalities in patients with β thalassaemia major. Wide osteoid seams with few osteoblasts before treatment with transfusion were replaced by narrower osteoid seams and a pronounced increase in osteoblasts.[18] There was also an increase in serum alkaline phosphatase activity.

In conclusion, the low or low-normal 25-OHD concentrations in patients with β thalassaemia major do not reflect pronounced abnormalities in vitamin D or calcium homeostasis. Nor is there any evidence of parathyroid hormone or calcium abnormalities in most patients with this condition. The skeletal abnormalities of thalassaemia are probably due to other mechanisms, and vitamin D supplementation is not likely to cause their resolution.

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Cord blood IgE and month of birth

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SUMMARY If cord blood IgE is used to detect those predisposed to become allergic it is important to define appropriately the normal values for this measurement. A commonly cited cut off point is 1·0 IU/ml. We analysed 5353 cord blood samples for IgE by means of an enzyme linked immunosorbent assay. Descriptive statistics of the distribution curve of cord blood IgE concentrations showed that most normal values were well below the cut off value of 1·0 IU/ml and that most abnormal values were in the neighbourhood of 1·0 IU/ml. It seems advantageous, therefore, to lower the cut off value for cord blood IgE.

When cord blood IgE was analysed according to the child's month of birth a significantly uneven distribution of abnormal cases of cord blood IgE concentrations over the year was found. The occurrence of an abnormal cord blood IgE concentration showed a significant cyclic trend, with a peak near the end of April and a trough in late October.

Allergy is a leading cause of morbidity in modern society. (Foucard T. The epidemiology of allergic disease in childhood. Presented at annual meeting of the European Academy of Allergology and Clinical Immunology, Stockholm, 1985.) Prediction of the disease is important because early avoidance of exposure to allergens can postpone or prevent clinical manifestations. Prolonged breast feeding, avoidance of allergens by the pregnant woman and the nursing mother, and gradual and delayed weaning to solid foods may be beneficial in this regard, at least temporarily.[1–7] This seems to be especially the case in at risk newborns—for example, those with low T cell counts,[7] a cord blood IgE concentration >1·0 IU/ml,[8] or a positive family history for allergy.[6] A prevention programme has to be started as early as possible. A family history of atopy and a high total cord blood IgE concentration are the best predictors of an allergic constitution.[1 8–11]

Neonatal screening of cord blood IgE concentrations seems warranted for all babies, or at least for the babies at risk because of a positive family history.[8–10] A cut off value of 1·0 IU/ml has been used in many studies, but lower values have been proposed.[[illegible] 8 10 11] In this study we evaluated statistically the distribution of cord blood IgE concentrations in the range below the cut off point of 1·0 IU/ml.

In addition, we report on the influence of month of birth on cord blood IgE concentrations. Fluctuations of the cord blood IgE concentration according to month of birth may have important implications in prevention programmes. A recent publication of Croner and Kjellman emphasised the importance of month of birth in the development of allergy.[12] The authors concluded that children with a high cord blood IgE concentration who were born in May had the highest risk of developing an allergic disease.

Patients and methods

Patients. Cord blood samples of 5838 newborns were examined during one year (1985). The children were born in the community hospitals of Genk, Bree, Waterschei, Heusden, Tongeren, Bilzen, Hasselt, and Neerpelt. These hospitals were responsible for 66% of the deliveries in 1985 in Limburg, a province in the north eastern part of Belgium. The province had 730 000 inhabitants and a birth rate of 11·6 per 1000 in 1985.

Data recorded for each delivery included name of mother and child, sex, month of birth, birth weight (to the nearest 10 g), and gestational age (presented as weeks completed from the last menstrual period). All patients with incomplete data, as well as all twins, were excluded from statistical analysis. Thus 326 patients were removed from the study. A high IgA concentration in the cord blood is an indicator for possible contamination with maternal blood, and thus a further 157 cord blood samples were excluded from further analysis. A further two patients were excluded as not enough cord blood was available for analysis.

Thus 5353 cord blood samples were finally included in the study, 2723 of them from boys. A total of 3975 of the children (74%) had two Belgian parents, 820 (15%) had two immigrant parents (mostly from south Europe and north Africa), and 558 (10%) had parents of mixed origin. Cord blood IgE concentrations did not differ significantly between these groups.

Methods. Cord blood serum was examined for IgE and IgA (among other variables) by means of a conventional microtitre sandwich enzyme linked immunosorbent assay (ELISA), as previously described.[13] The technique for IgE determination has a high reproducibility, is sensitive (detection limit of 0·01 IU/ml), and shows an excellent correlation with the conventional paper radioimmunoabsorbent test[14] and radioimmunoassay[15] for the concentration range where these techniques can be applied. Antibodies used on the solid phase were goat antihuman IgE (Tago) and rabbit antihuman IgA (Dako), respectively. Antihuman IgE monoclonal antibody (Hybritech) and rabbit antihuman IgA (Dako), conjugated with horseradish peroxidase, were used as second antibody, respectively

The samples were read on a multichannel spectrophotometer at 450 nm (Titertek Multiskan MC, Flow Laboratories), connected to a Commodore 8032-SK microprocessor.

The cut off point used for IgE was 1·0 IU/ml and for IgA was 32·3 μg/ml. The latter was calculated as the mean + 3 SD, as determined previously in a pilot study of newborns. (Bosmans E. Unpublished data.)

Statistical methods

Computation of the statistical analyses performed in this paper used the packages MINITAB (Pennsylvania State University) and BMDP-PC (Statistical Software Inc, University of California). Wherever appropriate, we used general descriptive statistical methods, correlation analysis, and the Edwards' test for cyclic trend.[16] As an alternative to the Edwards' test we could have used the method of Mardia,[17] but both tests, however, lead to the same conclusion.

As a result of the very skewed shape of the IgE histogram (Figures 1 and 2) we used the Kruskal-Wallis one way analysis of variance (ANOVA) test for the comparison of the sum of group ranks.[18]

Results

The total cord blood IgE concentration was determined in 5353 cord blood samples. Of these, 182 (3%) had an IgE concentration above 1·0 IU/ml. Figure 1 shows that most of the abnormal values are close to the cut off point. Of these 182 samples, 119 (65%) were lower than 2 IU/ml and 161 (88%) lower than 4 IU/ml. Higher cord blood concentrations were rare. Figure 2 shows the distribution of the IgE concentrations below or equal to 1·0 IU/ml Of the 5171 samples with IgE concentrations ≤1·0 IU/ml, 3747 (72%) had a concentration below 0·2 IU/ml and 4659 (90%) below 0·4 IU/ml. Only 512 (10%) serum samples with a normal cord blood IgE concentration had a value between 0·4 and 1·0 IU/ml, with clustering of the IgE concentrations towards the lower limit of this interval. As a result of the odd distribution pattern near the detection limit we did not attempt to fit a curve to the IgE histogram, although a log normal or gamma distribution seemed appropriate for the normal values.

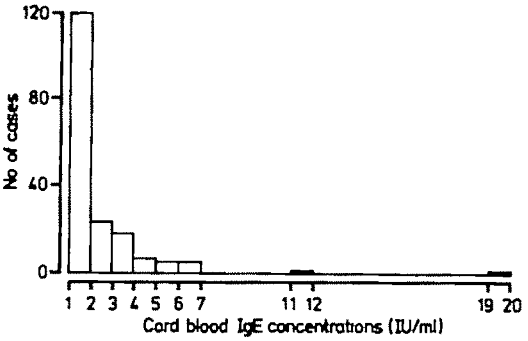

Fig. 1 *Histogram of the cases with abnormal cord blood IgE concentrations (>1·0 IU/ml) (n=182) The intervals are (left) open (right) closed. Each interval has a width of 1·0 IU/ml.*

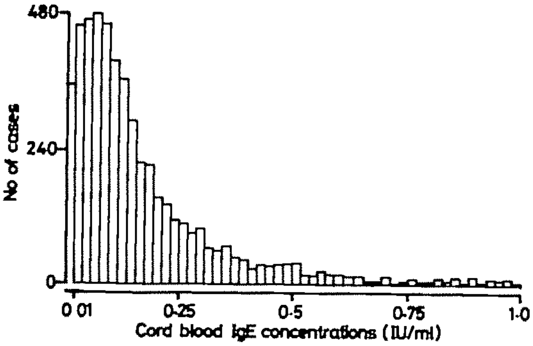

Fig 2 *Histogram of the cases with normal cord blood IgE concentrations (≤1·0 IU/ml) (n=5171) The intervals are (left) open (right) closed. Each interval has a width of 0·02 IU/ml, except the first and the last one (0·01 IU/ml)*

The mean cord blood IgE concentration for the whole population was 0·25 IU/ml, and the median was 0·12 IU/ml.

The cord blood IgE concentrations were then analysed according to month of birth. The number of abnormal values was unevenly distributed over the year. Figure 3 shows a plot of the number of samples with a IgE concentration above 1·0 IU/ml (the numbers were adjusted for the overall distribution of births over the whole year). A clear cyclic pattern emerged. A simple sinusoidal function was fitted using the Edwards' test ($p<0\cdot001$)[16] The resulting fit showed a maximum around late April and a minimum around late October. When the cut off point was lowered to 0·9, 0·8, or 0·7 IU/ml the same pattern emerged (Table 1). The number of normal cases (cord blood IgE ≤1·0 IU/ml) did not show any particular pattern as a function of the month of birth (data not shown).

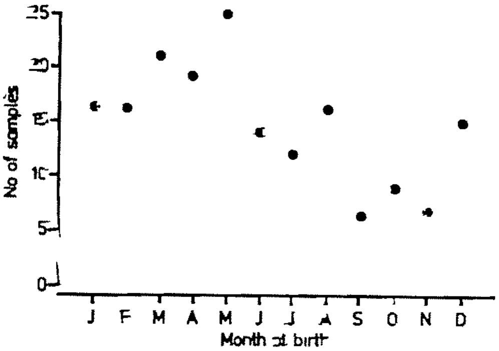

Fig 3 *Adjusted number of samples with a cord blood IgE concentration >1·0 IU/ml according to the month of birth. A sinusoidal curve can be fitted through these points and the difference is significant (Edwards' test=18·2, df=2, p<0 001).*

Table 1 *Edwards' test values and significance for different cut off points of cord blood IgE concentrations*

Cut off points (IU/ml)	*Edwards' test*	*Degree of freedom*	*p Value*
1 0	18 2	2	<0 001
0·9	21 2	2	<0·001
0 8	27 9	2	<0·001
0·7	29 6	2	<0 001

Next, the absolute values of cord blood IgE were analysed according to month of birth for two groups. Firstly, all samples were analysed together (group A). Then the group with a normal cord blood IgE concentration was analysed separately (group B). The group of abnormal cases (cord blood IgE >1·0 IU/ml) showed no significant difference in mean or median IgE concentrations between different months. The size of this group was too small, however, to pursue this point any further. For group A the difference in absolute cord blood IgE concentrations over the months was highly significant (Kruskal-Wallis, ANOVA test, $p<0\cdot0001$). The months with the greatest number of abnormal cord blood IgE concentrations (March, April, and May) also had the highest mean IgE concentrations. May was the most remarkable month, with a mean cord blood IgE concentration of 0·34 IU/ml and a median of 0·15 IU/ml (Table 2) The same trend was found when the normal IgE values were analysed separately (group B) (Kruskal-Wallis value=68·65, df=11, $p<0\cdot0001$) (data not shown).

Table 2 *No of births with normal and abnormal cord blood IgE concentrations and mean and median cord blood IgE concentrations according to month of birth*

Month of birth	*% (Cumulative %) Of total No of births (n =5353)*	*No (adjusted) with observed cord blood IgE*		*Absolute cord blood (IU/ml)*	
		Normal	*Abnormal*	*Mean*	*Median*
January	6 2 (6 2)	319 (429)	12 (16)	0 22	0 11
February	7 8 (14 0)	401 (428)	15 (16)	0 25	0 12
March	9 8 (23 8)	503 (428)	25 (21)	0 29	0 12
April	9·4 (33 2)	481 (426)	22 (20)	0 27	0 13
May	9 3 (42 5)	468 (419)	28 (25)	0 34	0 15
June	8 6 (51·1)	447 (433)	15 (15)	0 20	0 10
July	9 6 (60 7)	504 (437)	14 (12)	0 26	0 12
August	7 7 (68 4)	396 (429)	15 (16)	0 24	0 11
September	8 6 (77 0)	449 (435)	7 (7)	0 19	0 10
October	8 3 (85 3)	437 (439)	9 (9)	0 20	0 11
November	7 0 (92 3)	358 (438)	6 (7)	0 22	0 12
December	7 7 (100·0)	398 (431)	14 (15)	0 25	0 13
Total		5171	182*	0 25**	0 12**

*Edwards' test value=18 2, df=2, p<0 001

**Absolute cord blood mean and median, Kruskal-Wallis value=76·24, df=11, p<0 0001

Discussion

Cord blood IgE, which seems to be the single best predictor of allergy,[10 19] was greater than the cut off value of 1·0 IU/ml in 3% of newborn babies in this study. This percentage is lower than reported elsewhere.[8 9] The mean cord blood IgE concentration was 0·25 IU/ml. Infants with cord blood IgE concentrations below 1·0 IU/ml had mostly very low concentrations; 90% of all normal values fell below 0·4 IU/ml. Only a tenth of the samples fell between 0·4 and 1·0 IU/ml. The sensitivity of the screening method might be increased, with little effect on the selectivity, by lowering the cut off limit to 0·9 or even 0·7 IU/ml if it is assumed that nearly 15% of children develop atopic disease during childhood and adolescence.[6] A lower cut off may therefore identify a greater percentage of the at risk population. Most of the abnormal cord blood IgE concentrations are clustered near the cut off point of 1·0 IU/ml, with only a few high values. Sixty five per cent of the abnormal cord blood IgE values were situated between 1 and 2 IU/ml. These observations are an important argument for the cut off point for normal cord blood IgE values to be lowered. Prospective clinical follow up studies have already substantiated this point of view [3 9 10]

To detect seasonal influences, cord blood IgE concentrations were analysed according to month of birth. We found a cyclic distribution of the number of abnormal cord blood IgE values over the year. The peak of the sinusoidal curve was situated in the spring (March, April, and May), while the trough was in late October Not only did we find that more newborns had an abnormal cord blood IgE concentration in spring, but we also found higher overall absolute cord blood IgE concentrations in this season. The non-homogeneity of proportions of abnormal cord blood IgE values over the year does not explain this difference of absolute values according to the month of birth. The difference remained significant when the abnormal values were omitted (group B). Thus it seems that to be born in a particular season carries a high relative risk for an abnormal cord blood IgE concentration and hence a higher risk for the development of an allergic disease.

Until recently, most of the studies published about hypersensitivity in correlation with month of birth used selected patient populations who either already had an allergic disease[20–22] or were predisposed to becoming diseased because of a positive family history.[23] The study of Croner and Kjellman addressed the importance of month of birth together with a high cord blood IgE concentration in relation to the development of allergy.[12] Both indices seemed to influence the incidence of atopic disease. But cord blood IgE as such was not evaluated as a function of the month of birth. From our study it seems that month of birth influences the IgE concentration in the cord blood, so that we find a cyclic sinusoidal pattern with higher cord blood IgE values in the spring together with a greater percentage of abnormal values. The reason for this is as yet unclear. Many factors may be involved. The immune regulation of IgE production is only partly understood. It was not the aim of this study to explore the mechanism behind these significant differences, and further study is certainly needed. Intrauterine sensitisation can probably trigger an IgE mediated response in the newborn.[4] Highly sensitive antigen specific IgE determination in cord blood (against pollen antigens and others) may become a tool in future research.

From this study we conclude that there is a difference in cord blood IgE concentration in relation to month of birth. This is true both for abnormal values, which show a cyclic sinusoidal pattern over the year, with a peak near the end of April and a trough in late October, and also for the absolute concentration of cord blood IgE, which is higher in the spring and lower in the autumn.

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Normal values for urinary *N*-acetyl-beta-glucosaminidase excretion in preterm and term babies

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SUMMARY Urinary *N*-acetyl-beta-glucosaminidase (NAG) excretion was measured in 14 healthy, preterm, male neonates with gestational ages between 32 and 35 weeks. Daily NAG excretion increased significantly during the first four weeks of life. No correlation was observed between urinary NAG:creatinine ratio and postnatal age regardless of whether measurements were taken from the whole 24 hour urine collection or from an isolated urine spot sample at the same time on each day. When the preterm infants were compared with a group of 20 healthy, full term, male infants at a postnatal age of 7 days the NAG:creatinine ratio was significantly higher in the preterm group, the measurements having been taken from single urine spot samples. We suggest that this variable be used in the evaluation of renal tubular integrity during the neonatal period.

Renal anatomic integrity can be reflected in the output of urinary enzymes.[1] Of these enzymes, *N*-acetyl-beta-glucosaminidase (NAG) may be of greatest interest as it is present in appreciable amounts in the proximal tubular cells.[2] The molecular weight of NAG is about 140 000 daltons.[3] Enzymes with molecular weights that exceed 70 000 daltons are not normally filtered into the urine.[4]

Increased urinary excretion of NAG has been found to be correlated with tubular damage in children with a variety of renal diseases.[5 6] In adults urinary excretion of NAG has been shown to be a good predictor of aminoglycoside toxicity to the tubular epithelium.[7] Few data are available on the urinary excretion of NAG in neonates who present with renal damage.[5 6 8 9] Parini *et al* used NAG excretion in the neonatal period as a predictor of possible renal toxicity during treatment with amikacin. They gave no information, however, about the normal excretion of this enzyme in growing preterm newborns.[10]

The purpose of this study was to measure the urinary excretion of this lysosomal enzyme in healthy preterm babies and to investigate whether the urinary NAG excretion is influenced by postnatal age.

Patients and methods

Renal function and urinary NAG excretion were evaluated in 14 healthy neonates whose gestational ages were between 32 and 35 weeks.[11] Gestational age was assessed according to the Finnstrom score.[12] Only male infants were recruited due to the difficulties in obtaining precise 24 hour urine collections in girls. Infants were excluded if they had any of the following conditions: nephrotoxic drugs administered to the mother during the final trimester, Apgar score below 7 at one minute, respiratory distress syndrome, infectious diseases, any drugs in the neonatal period, episodes of hypotension or hypertension according to Bucci's criteria, serum bilirubin concentration >206 µmol/l, and patent ductus arteriosus. Fluids were administered as follows: 60 ml/kg/day on day 1, 80 ml/kg/day on day 2, 100 ml/kg/day on day 4, 130 ml/kg/day on day 6, and 150–180 ml/kg/day from day 8 onwards. Parenteral fluids (10% dextrose and electrolytes) were given from day 1 to day 5. A formula adapted for preterm neonates was introduced as soon as intestinal tolerance was observed.

A 24 hour urine collection was obtained on days 1, 7, 14, 21, and 28, using an adapted urine collection bag. The collection period was carefully timed. Determinations of creatininuria and enzymuria were calculated in terms of absolute rate of excretion (total amount excreted/collection time).

NAG was measured in the whole 24 hour urine collection as well as in a single urine spot sample taken at the same time on each day and immediately frozen at −20°C. NAG activity does not deteriorate when frozen and is not affected by either bacteriological colonisation or storage for several hours at 4–5°C.[13] The urine NAG activity was determined by the method of Maruhn.[14] Plasma and urine concentrations of creatinine were determined by Jaffe's reaction after deproteinisation (Boerhinger).[15] NAG excretion was expressed as µmol/24h for the 24 hour collection and in µmol/l for the single urine spot sample. Creatininuria was determined from the same whole 24 hour urine collection (mmol/24h) and urinary creatinine concentration measured from each urinary spot sample (mmol/l).

We also compared the NAG excretion at a postnatal age of 7 days between these preterm babies and a group of 20 healthy, appropriate of gestational age, full term male neonates, the measurement being taken this time in both groups from single urine spot samples only. These term infants were breast or bottle (infant formula) fed by their mothers in the nursery.

Glomerular filtration rate, as estimated by the creatinine clearance in the 14 preterm infants and by the Schwartz formula in the 20 full term infants, was within the normal range of published values for all infants,[16–18] confirming that our subjects had normal renal function.

Statistical analysis was performed using Student's *t* test, comparison between two independent correlations test, comparison between two mean values with standard deviation, and χ^2 test with Yates's correction.

Results

Longitudinal study in preterm infants showed a significant increase in urinary NAG excretion/24h during the first four weeks of life (r=0·59; p<0·001) (Fig. 1). Similarly, the daily creatininuria also showed a significant increase with postnatal age (r=0·38; 0·02<p<0·05), so that when expressed as daily NAG excreted/unit of creatinine excreted (µmol/mmol) there was no change with postnatal age (r=0·27; p>0·05) (Fig. 2).

Moreover, the NAG:creatinine ratio (µmol/mmol) was the same in preterm infants whether measured in urine spot samples or 24 hour speci-

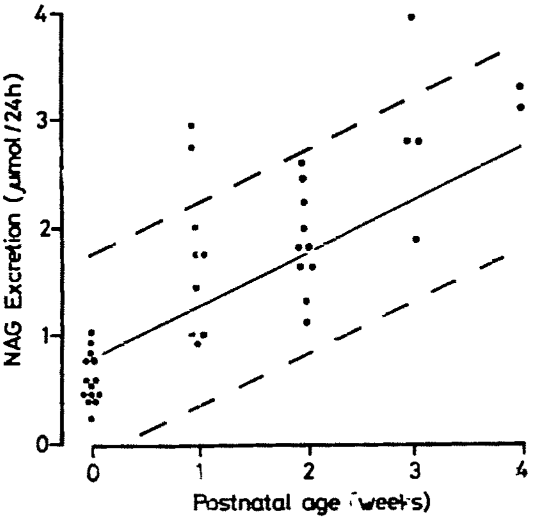

Fig. 1 *Urinary N-acetyl-beta-glucosaminidase (NAG) excretion over 24 hours in relation to postnatal age in preterm neonates with a gestational age between 32 and 35 weeks. (Standard deviation y=0·728+1·[illegible]4 10^{-2} × x r=0·59, p<0·001).*

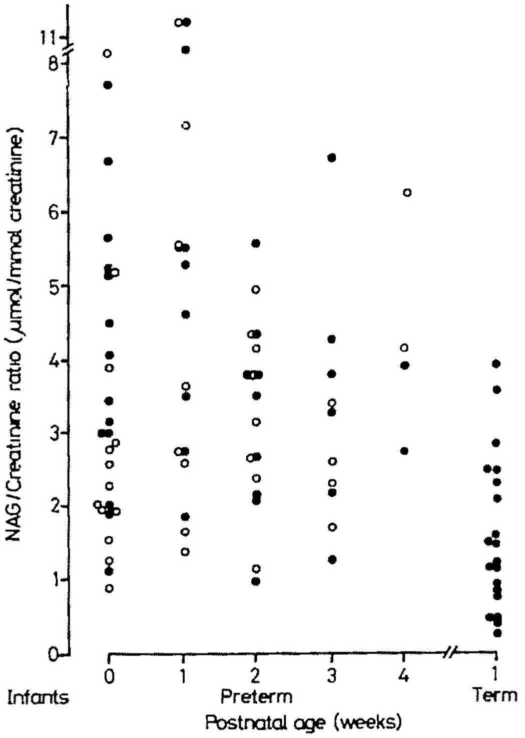

Fig. 2 *Urinary N-acetyl-beta-glucosaminidase (NAG) creatinine ratio in relation to the first four weeks of life in preterm neonates with gestational age between 32 and 35 weeks and in full term babies at a postnatal age of 7 days Measurements were taken in the preterm group from the whole 24 hour collection (○) (total amount excreted/collection time) (r=0·27; p>0·05) and from a single urine spot sample (●) (r=−0·066; p>0·1). The measurements in the term group were taken from a single urine spot sample only*

Table *Measurements of urinary NAG excretion taken from 24 hour collection or from spot sample in preterm and term infants*

Urinary NAG excretion (µmol/mmol creatinine)	*Preterm group*		*Term group*
	24 Hour diuresis (n=35)	*Spot sample (n=39)*	*Spot sample (n=20)*
Mean (SD)	3·6 (2·39)	4·43 (2·41)	1·75 (1·1)
	NS	p<0·001	
5th–95th Centile limits	0·9–9·7	1·2–9·8	0·4–4·3

NAG=*N*-Acetyl-beta-glucosaminidase, NS=not significant

mens (p>0·05), and this ratio calculated on a single urine spot sample also remained stable during the four weeks of the study (r=−0·066; p>0·1) (Fig. 2).

The NAG·creatinine ratio measured in a single urine spot sample on the seventh day of life was significantly higher in preterm infants than in term infants (mean (SD) ratios 4·9 (2·9) µmol/mmol and 1·75 (1·1) µmol/mmol, respectively; p<0·001).

The 95th centile limits for the NAG·creatinine ratios in the preterm babies during the four weeks were 9·8 µmol NAG:mmol creatinine and in the term week old infants were 4·3 µmol NAG/mmol creatinine (Table)

Discussion

Urinary excretion of *N*-acetyl-beta-glucosaminidase has been studied extensively in adults suffering from renal diseases.[1 3 7 17] This enzyme meets all the criteria of Gonick *et al* for selecting enzymes that may be useful in detecting renal tubular damage and seems to be a good indicator of renal tubular cell integrity.[17] In particular, increased urinary excretion of NAG can be a good predictor of aminoglycoside toxicity to the proximal tubular epithelium.[7]

In fact, Morin *et al* considered that the site of the toxic action of an aminoglycoside such as gentamicin was exclusively the lysosome of the proximal cell.[2] Lysosomal overloading can lead to disruption of its membrane and subsequently to cell death.[2] Increased NAG excretion has been observed in children who present with well characterised tubulointerstitial disease. This phenomenon seems to be more important in girls aged under 2 years.[5]

Few data are currently available on the normal excretion of NAG in healthy preterm and full term infants.[1 6] All infants enrolled into this study were healthy and had a normal glomerular filtration rate.[16 18]

Our data indicate that NAG excretion in neonates reaches much higher values than in adults. Our results also indicate that NAG excretion at a postnatal age of 7 days is lower in full term babies than in preterm babies This agrees with previous reports.[6] We have shown a rise in absolute urinary NAG excretion/24 hours with postnatal age.

The NAG:creatinine ratio showed no correlation with postnatal age in the preterm babies. Similarly, no correlation was observed between the NAG·creatinine ratio and increasing postnatal age when the measurements were taken from an isolated single urine spot sample in the same group of preterm infants. Many authors have routinely used creatininuria as a denominator to avoid urine collection.[6 7 14 17] This mode of expression has been criticised with regard to the neonatal period because of the age dependent changes in the creatininuria.[19] Nevertheless, our data suggest this determination to be accurate for routine use.

The value of using an increase in urinary NAG excretion as an indicator of renal tubular damage in the neonatal period, as has been done for adults and older children, remains to be tested. This is presently under investigation in newborn infants who have suffered severe episodes of asphyxia as well as in those who have received potentially nephrotoxic drugs.

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Infant mortality in southern Brazil: a population based study of causes of death

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SUMMARY The causes of 215 infant deaths occurring in a population based cohort of 5914 infants from southern Brazil were determined. Perinatal problems were responsible for 43% of these deaths and infectious diseases for 32%. In the group who died of infectious diseases, respiratory infections and diarrhoea were equally important, each accounting for 12% of all deaths.

A total of 87% of the deaths occurred in the first six months of life, and this proportion remained high (77%) even after perinatal causes had been excluded. On the other hand, 53% of the infants who died were of low birth weight, as opposed to 7·9% of the survivors. This suggests that low birthweight infants need to be carefully followed by health workers at primary level, especially during the first six months.

It was estimated that if the incidence of low birth weight was reduced from the present 8·8% to 5% the likely reduction in infant mortality would be 20%. This reduction would be 33% for deaths due to perinatal causes, 14% for respiratory infections, and only 5% for diarrhoea.

Efforts for the prevention of infant deaths in southern Brazil are more likely to be effective if they concentrate on improving perinatal health care and environmental conditions.

The prevention of infant mortality is widely recognised as a social and health priority in developing countries For many of these countries, however, important information about infant deaths, which is much needed for effective prevention, is not available. Ashworth and Waterlow reviewed this subject in 1982[1] and were unable to find any national data on infant mortality from developing countries except for the inter-American study published in 1973.[2] These authors emphasised that more information is needed about the causes of deaths and age distribution of infant mortality.

Reasons for the paucity of information include the lack of population based epidemiological studies of infant mortality in developing countries and the poor quality of vital statistics. In the latter case the data are often unsatisfactory because of under registration, the poor ascertainment of causes of death, and the lack of information about potentially important risk factors, such as birth weight.

A longitudinal study of child health has been in progress since 1982 in the city of Pelotas in southern Brazil (population 210 000), and 5914 children are being followed from birth. The study of this cohort allowed us to analyse specific aspects of infant mortality. In this paper we attempt to answer the following questions:

(a) What are the causes of infant deaths?
(b) What is the age distribution of deaths due to different causes?
(c) What is the role of low birth weight in deaths due to different groups of causes?

A better understanding of these issues may help health planners to focus on infants who are at greatest risk.

Patients and methods

The study cohort comprised all 5914 liveborn babies delivered in the three hospitals in Pelotas in 1982 whose mothers lived in the urban area. These represented more than 99% of all births that occurred in the city that year.[3] All mothers were interviewed soon after delivery and their babies were followed up during their stay in hospital. As babies are discharged from hospitals very early (23% within 24 hours) it was necessary to visit a 20% random sample of them at home after one week of life to check their state of health after the perinatal period

In early 1984 we attempted to find all children through home visits when their ages ranged between 12 and 27 months (average 20 months). As a high proportion of families had moved within the city since the children had been born all 69 000 households in the city had to be visited in search of children born in 1982.

During the home visits information on infant deaths was solicited. In addition, we surveyed all deaths reported at hospitals, registries, and health authorities in Pelotas as well as in neighbouring cities and the state's capital. Causes of death were determined by reviewing hospital case notes, death certificates and necropsy reports, as well as by interviews with relatives of the dead children during home visits.

Deaths were grouped into the following causes according to the *International classification of diseases*[4]: perinatal (ICD codes 760–779·9), malformations (ICD codes 740–759·9), respiratory infections (ICD codes 460–519·9), diarrhoea (ICD codes 001–009·3), other infections (ICD codes 010–139·8 320–325,382,383,573·3,590,595,599,680–686), ill defined (ICD codes 780–799·9), and other causes.

The denominators (infant years at risk) for the rates presented below were calculated by actuarial methods, assuming that infants who were not located had been followed for half a year. Confidence intervals for the relative risks were calculated by Miettinen's method.[5]

Results

Of the original cohort of 5914 babies, 233 were found to have died (215 of whom died in the first year) A total of 750 (13%) could not be located, and so 4931 babies were examined. The infant mortality was 38·8 per 1000 live births. The neonatal and post-neonatal mortalities were 21·5 and 17·3 per 1000 live births, respectively. The official infant mortality calculated by the State's Secretary of Health was 24% lower, due to under registration of infant deaths.[6]

Causes of infant death. Perinatal causes were responsible for 43% of infant deaths and infections for 32% (Table 1). In this group of deaths due to infections, respiratory infections and diarrhoea were equally important, each accounting for 12% of deaths. Malformations were the third most important cause (13%), followed by ill defined causes (11%). In this group, nine (4%) cases were presumed sudden infant deaths.

Risks of infant deaths according to birth weight and groups of causes. More than half (53%) of the infants who died were of low birth weight (LBW), whereas 8·8% of the whole cohort were of LBW.[7] Table 1 shows the cause specific relative risks of death associated with LBW. LBW infants were 35·9 times more likely to die due to perinatal causes than babies of appropriate birth weight. For infectious causes, the relative risks of infant mortality associated with LBW were 6·7 (95% confidence intervals =3·0–14·9) for respiratory infections, 2·5 (95% confidence intervals=0·9–6·7) for diarrhoea, and 2·9 (95% confidence intervals=1·0–8·3) for other infections. We also calculated what would be the reduction in the cause specific and overall infant mortality if the incidence of low birth weight was reduced from the present 8·8% to 5%, which is the goal set for the United States for 1990.[8] If that occurred a reduction of 20% in infant mortality would be expected. This reduction would be 33% for deaths due to perinatal causes, 14% for respiratory infections, and only 5% for diarrhoea

Table 2 shows the risks of death associated with LBW at different ages during the first year LBW babies comprised 71% of babies who died in the neonatal period and were 23·9 times more likely to

Table 1 *Infant mortality in Pelotas, Brazil, 1982–83, showing causes of death, relative risks associated with low birth weight, and estimated reduction in infant mortality if the incidence of low birth weight was reduced to 5%*

Causes of death	*No (%)*	*Rate/1000*	*Relative risk associated with low birth weight (95% confidence intervals)*	*% Reduction in mortality assuming low birth weight reduced to 5%*
Perinatal*	92 (43)	16·6	35·9 (25·9–49·6)	33
Malformations	27 (13)	4·9	—	—
Respiratory infections	25 (12)	4·5	6·7 (3·0–14·9)	14
Diarrhoea	25 (12)	4·5	2·5 (0·9–6·7)	5
Ill defined†	24 (11)	4·3	5·0 (2·3–10·8)	12
Other infections‡	18 (8)	3·3	2·9 (1·0–8·3)	6
Other causes	4 (2)	0·7	3·3 (0·4–28·1)	3
All causes	215 (100)	38·8	11·0 (8·7–14·4)	20

* Prematurity and hyaline membrane (60 cases), asphyxia (16), infection (12), and other causes (four)

† Presumed sudden infant death syndrome (nine cases) and other ill defined diseases not helped by doctors (15)

‡ Sepsis (14 cases) and meningitis (four)

Table 2 *Infant mortality at different ages in the first year of life, showing relative risks associated with low birth weight and estimated reduction in infant mortality if low birth weight was reduced to 5%*

Period and age at death	*No (%)*	*Rate/1000*	*Relative risk associated with low birth weight (95% confidence intervals)*	*% Reduction in mortality assuming low birth weight reduced to 5%*
Early neonatal (0–6 days)	96 (45)	17·3	26·8 (19·6–36·8)	30
Late neonatal (7–27 days)	23 (10)	4·2	15·5 (8·6–29·1)	23
Neonatal (0–27 days)	119 (55)	21·5	23·9 (18·0–31·9)	29
Early post-neonatal (1–5 months)	68 (32)	12·3	5·1 (3·2–8·1)	11
Late post-neonatal (6–11 months)	28 (13)	5·0	2·7 (1·1–6·5)	6
Post-neonatal (1–11 months)	96 (45)	17·3	4·3 (2·9–6·5)	10
Infant (0–11 months)	215 (100)	38·8	11·0 (8·7–13·9)	20

die in the first month than babies with birth weights of 2500 g or more The reduction in incidence of LBW from 8·8% to 5% would, theoretically, reduce neonatal mortality by 29%. As expected, LBW infants comprised a lower proportion (30%) of postneonatal deaths, the relative risk of postneonatal death associated with LBW being 4·3 (95% confidence intervals=2·9–6·5). The predicted reduction of deaths in this period associated with the reduction of LBW to 5%, therefore, would be only 10%.

Age distribution of infant deaths by groups of causes. Table 2 shows that 45% of infant deaths occurred during the first week of life (17% during the first day) and an additional 10% were late neonatal deaths (7–27 days). Deaths in the first six months of life accounted for 87% of the total infant mortality.

Table 3 shows that the excess of deaths in the first month of life was due largely to perinatal causes. In fact, all but two of the deaths from perinatal causes occurred in the first four weeks of life, and 90% occurred during the first week. In addition, 67% of deaths caused by malformations occurred in the first month. A somewhat different pattern of age distribution was observed for the remaining causes. After deaths from perinatal causes and malformations had been excluded only 11% of deaths occurred in the neonatal period, whereas 62% occurred in the early post-neonatal period (1–5 months). For infectious causes, 64% of deaths caused by respiratory infections, 84% by diarrhoea, and 78% by other infections occurred in the first six months.

Discussion

An advantage of this population based cohort study was that it derived the number and causes of infant deaths not only from official information but also from interviews with the parents of the dead infants and from reviews of hospital case notes, death certificates, and postmortem examinations. This emphasis on the careful ascertainment of the causes of death resulted from the findings of previous studies in Latin America, which have shown that many diagnoses contained in death certificates do not agree with other clinical information.[2]

Table 3 *Infant deaths at different ages according to cause Values are No (%)*

Causes of deaths	*Age at death*			*All deaths*
	0–27 days	*1–5 months*	*6–11 months*	
Perinatal	90 (98)	2 (2)	—	92
Malformations	18 (67)	6 (22)	3 (11)	27
Respiratory infections	3 (12)	13 (52)	9 (36)	25
Diarrhoea	—	21 (84)	4 (16)	25
Ill defined	4 (17)	13 (54)	7 (29)	24
Other infections	3 (17)	11 (61)	4 (22)	18
Other causes	1 (25)	2 (50)	1 (25)	4
All non-perinatal	29 (23)	66 (54)	28 (23)	123
All causes	119 (55)	68 (32)	28 (13)	215

Although this study was carried out in an urban area of a middle income country, and deaths occurred predominantly in hospitals, 24% of the deaths failed to reach the official death registration system. This shows that this system needs to be thoroughly revised and reinforces the need for using alternative sources of information in studies of infant mortality.

A better understanding of the causes of infant deaths in Pelotas may be obtained by a comparison with other countries. In Table 4 we compare our cause specific distribution of infant deaths with that of England and Wales in 1980.[9] The infant mortality was 3·4 times higher in Pelotas than in England and

Wales, and in both places perinatal causes ranked first in importance, accounting for about 40% of infant deaths The mortality from perinatal causes was 3·7 times higher, however, in Pelotas than in England and Wales. As the differences in the incidence of low birth weight are not so pronounced (8·8% and 6·8%, respectively[9] it seems that this higher mortality can be largely ascribed to inadequacies in perinatal health care It is therefore important to improve perinatal care, which means increasing the coverage and quality of antenatal care, the management of high risk mothers during labour and delivery, and the help being given to newborns in the delivery room. These goals are in conflict with the situation currently seen in Pelotas and many other Third World cities, where the best trained doctors are more often involved in delivering low risk mothers and looking after their babies, whereas high risk mothers are usually helped by less well trained midwives.[10 11]

Infectious diseases represented the second most important cause of death in Pelotas, being 8·7 times more common than in Britain. In fact the infant mortality from infectious causes in Pelotas (12·2/1000) was higher than the overall infant mortality in Britain (11·4/1000). A large proportion of these deaths due to infectious diseases may be prevented through enviromental and nutritional improvements as well as through better health care.

With regard to the age distribution of infant deaths, 87% occurred in the first six months of life, even higher than the 79% described by Puffer and Serrano for 13 projects in eight Latin American countries[2] and the 80% reported for Ghana.[12] When only non-perinatal causes are considered the proportion of infant deaths occurring in the first six months is still high (77%). This indicates that most of the preventive efforts of health workers should be concentrated on this period of increased risk.

We estimated a likely reduction of only 20% in the infant mortality if the incidence of low birth weight in Pelotas was reduced to 5%, which is a rather ambitious goal. For non-perinatal causes of death, this reduction would be even smaller (11%). The prevention of low birth weight is a top priority for further reducing the infant mortality in developed countries, where many of the environmental and health care problems have already been solved.[8 13 14] In places like Pelotas, however, environmental changes and improvements in the quality and coverage of the health care system are probably more important than trying to reduce the incidence of low birth weight.

On the other hand, in terms of case management at health clinics, there is no doubt that low birth weight is an important risk marker, as low birthweight infants have an increased risk of dying. Health workers at the primary level must keep close contact with such infants, especially during the first six months.

Table 4 *Infant mortalities according to cause A comparison between Pelotas, Brazil (1982–3), and England and Wales (1980)*[9]

Causes of death	*Infant mortality*		*Ratio*
	Pelotas	*England and Wales*	
Perinatal	16·6	4·5	3·7
Infections	12·2	1·4	8·7
Malformations	4·9	3·0	1·6
Ill defined	4·3	1·5	2·9
Other causes	0·7	1·0	0·7
All causes	38·8	11·4	3·4

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Baby walkers . . . time to take a stand?

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SUMMARY Experience in our hospital and figures from the Home Accident Surveillance System indicate that the number of accidents involving baby walkers is increasing. Safety specifications issued by the British Standards Institution are rarely, if ever, met in full by manufacturers. Home accident prevention measures have been shown to be of limited benefit. We advocate more stringent implementation of safety features in the design of baby walkers.

Personal observation suggested that our hospital was treating an increasing number of injuries associated with the use of baby walkers. We report three cases of accidents of this kind. All were admitted to this hospital within a recent three month period.

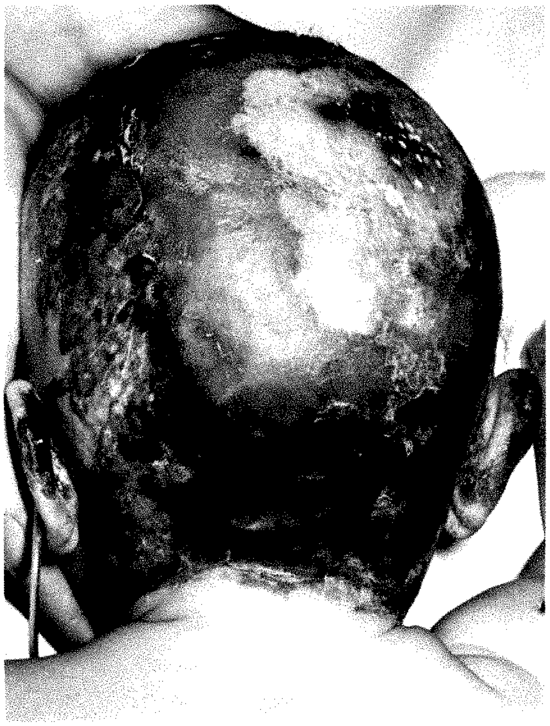

Fig. 1 *Head of case 1 at presentation, showing full thickness burns over two thirds of his scalp and 6×7 cm area of exposed skull vault at pole of occiput.*

Case reports

Case 1. A 7 month old boy was admitted to the burns unit after sustaining full thickness burns to the scalp apparently as a result of tipping backwards into an open fire while in his walker (Fig. 1). At the time of the accident he was accompanied only by his sister, who was less than 3 years old. Examination revealed full thickness burns over two thirds of his scalp. At the pole of the occiput there was an area of exposed skull vault measuring 6×7 cm, which was later found to be non-viable. His initial course was stormy and in the ensuing four months he underwent seven major surgical procedures. He eventually recovered without neurological deficit. There was a large area of scalp, however, that remained hairless.

Case 2. A 5 month old boy was admitted to the surgical ward after he had fallen part way down a flight of stairs in his walker. His fall was broken by his mother. He banged his head but did not lose consciousness. Examination revealed a drowsy child with a swelling on the right side of his head. *X* ray film confirmed a linear fracture of the parietal bone. He was detained in hospital for 48 hours and observations remained stable. Outpatient review three months later revealed no abnormality and he was discharged.

Case 3. A 7 month old boy was admitted to the surgical ward after sustaining injuries to his head and right arm. A short time previously he had been travelling in his walker when it tipped over a step in the kitchen, thrusting him forwards between a wall and a door. He was alone at the time of the accident. He screamed but subsequently became drowsy.

Examination revealed a swelling in the left temporofrontal region together with swelling and abrasion of the left forearm. *X* ray films of the skull and forearm revealed no bony injury. He was observed for 48 hours and remained well. At outpatient review six weeks later he was thriving and was discharged.

Discussion

There have been a number of reports in recent years on children's home safety and accident prevention,[1-5] but there have been few dealing specifically with baby walkers. Reports from the United States in 1982 called attention to the dangers of baby walkers.[6 7] We present evidence that such injuries are an increasing problem in this country also.

Baby walkers are devices that provide preambulatory infants with postural support in addition to offering them the opportunity to experience bipedal locomotion. They are intended to simulate independent walking and by so doing, it is argued, encourage and even accelerate the early acquisition of this skill. Without doubt they provide a number of infants with some amusement for many hours, allowing the parent and child a level of independence previously unavailable. It is not difficult to imagine that this very independence, so suddenly acquired, might lead to occasional lapses of attention on the part of a harassed adult.

The design of baby walkers is variable. Most have a seat or perineal strap, which is suspended from a rigid or folding frame. The frame is supported on a number of wheels or castors. Some designs include a small table surface for food and playthings. It is only recently that these devices have become commonplace; 30 years ago they were rarely found in any but the most privileged home. Nevertheless, a design that is currently popular has much in common with a Victorian example (Figures 2 and 3).

Figures for accidents in the home have been gathered by the Home Accident Surveillance System (HASS) since its inception by the Department of Trade in 1977.[8] Accident data, gathered from 20 participating accident and emergency departments in England and Wales, are published annually by HASS.[5] Figures for accidents that involve baby or child furniture and transport devices are presented in the Table. Figure 4 is a graph for accidents that specifically involved baby walkers. Baby walkers were involved in a much larger number of accidents in 1984 than they were in 1977, rising by a factor of 235%. Over the same period accidents that involved all baby and child transport devices rose by a factor of 128% and those that involved baby and child furniture by 118%. In 1977 accidents with baby walkers comprised 13·5% of accidents that involved baby and child transport devices. In 1984 this figure was 20·2%. Safety standards recommended by the British Standards Institution (BS 4648)[9] (but not enforceable by law) have undoubtedly improved safety margins, but by their widespread use baby walkers are an increasingly common cause of injury in the preambulatory infant.

Laws concerning the use of appliances and devices within the home are almost impossible to enforce. 'Official recommendations' rarely attract a satisfactory level of compliance. Even in the emotive and

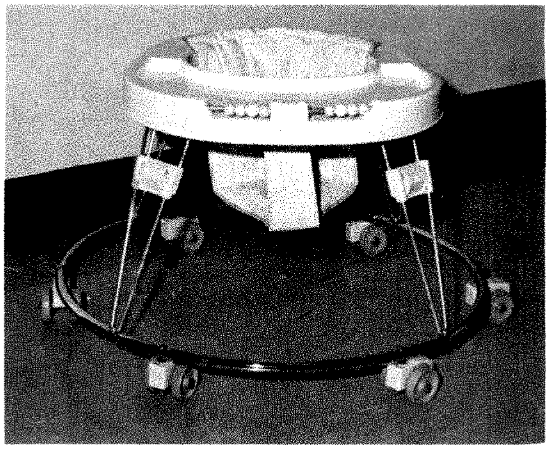

Fig. 2 *A popular modern baby walker, showing typical design features of a seat suspended from a rigid frame, which is supported on a number of wheels. There is also a small table surface. (Compare with Fig. 3.)*

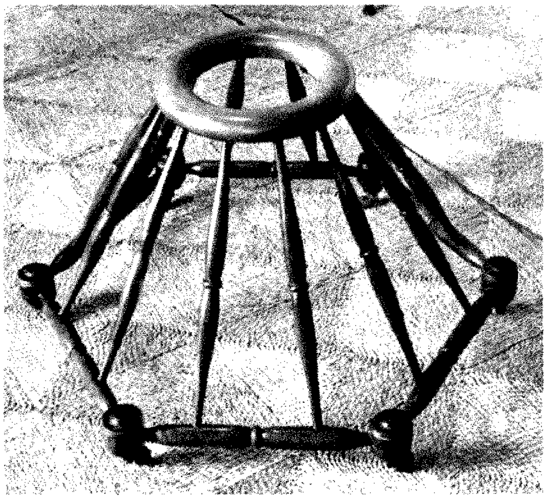

Fig. 3 *A Victorian baby walker, showing the similar basic design features to modern baby walkers. (Compare with Fig. 2.)*

Table *Incidence of accidents involving baby walkers and other baby furniture and transport devices (data from Home Accident Surveillance System 1977–84)*

Year	*Total No of accidents (all ages)*	*Accidents involving*			*Baby walker accidents as*	
		Furniture and transport devices	*Transport devices*	*Baby walkers*	*% Of transport only*	*% Of furniture and transport*
1977	77616	571	284	77	27·1	13·5
1978	67805	509	245	75	30·6	14·7
1979	69007	608	256	84	32·8	13·8
1980	105299	913	448	143	31·9	15·7
1981	122428	1274	620	249	40·2	19·5
1982	104126	1023	512	205	40·1	20·0
1983	98878	996	484	191	39·5	19·2
1984	110254	1275	650	258	39·7	20·2

'Furniture' includes cots, baby chairs, baby bouncers, bouncing cradle, play pens, potties, baby baths, safety gates, changing mats, and others
'Transport devices' include prams, pushchairs, buggies, carry cots, safety harness/reins, baby walkers, baby slings, and others

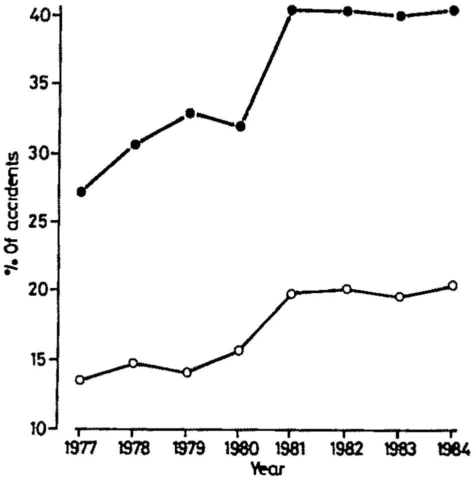

Fig 4 *Percentages of child and baby accidents that involved baby walkers for 1977–84* ●——●=*Percentage of transport accidents that involved baby walkers,* ○——○=*percentage of transport and furniture accidents that involved baby walkers*

potentially lethal area of infant restraint in motor vehicles, a recent study revealed that only 40% of a sample complied with official recommendations.[10] The British Standards Institution recommends that safety warnings be placed on both the packaging and the product instruction sheet of baby walkers.[9] They should include specific advice about never leaving the infant unattended and never using the device near steps, stairs, domestic fires, or hot appliances.[9] Despite this, most accidents occur in circumstances that contravene the written warnings [11] Between 80% and 90% of injuries that require admission to hospital follow falls down steps or stairs.[11–13] Up to 20% of infants are unaccompanied at the time of injury [11 13] Warnings on packaging or instruction sheets are notoriously easy to ignore or forget, and it could be argued that in the excitement of seeing baby take his 'first steps' parents might be even more liable to such an oversight. The British Standards Institution, however, also recommends that a safety warning be inscribed or stamped in permanent bold red lettering on a white background on the baby walker itself (namely 'WARNING. NEVER LEAVE YOUR BABY ALONE IN THIS WALKER'). Few models at present comply with this recommendation, yet a prominent warning so situated would be a daily reminder of potential hazards long after initial excitement has subsided.

Currently, there is no obligation on the part of designers or manufacturers of baby walkers to comply with the recommendations of the British Standards Institution nor on the part of retailers to ensure that they have been met. A recent investigation by the Trading Standards Department in this city, prompted by an increasing volume of complaints from the public, concluded that 'none of the models examined has been found to comply fully with British Standard 4648'. (Mawdsley PJ. Personal communication.) In these times when the law demands that our motor vehicles are roadworthy, that we are strapped in or helmeted, and have a certificate of competence to drive it seems strange that we do not insist through legislation on the same standards of safety for our dependent infants, this youngest group of 'drivers'.

The recommendations of the British Standards Institution on baby walker design concentrate largely on stability, as overturning is a common factor in most serious accidents.[6 7 11–14] Although few models meet the recommendations in full, a large number are intrinsically stable We believe, however, that overturning must always be considered a potential hazard. If these devices are to remain freely available further consideration should be given by designers not only to walker stability but also to infant protection in these almost inevitable accidents.[14]

Whether public education on home accident prevention produces any real benefit or not remains a matter of some contention. The effects of television programmes and health education campaigns specifically dealing with children's home safety have been investigated and have produced equivocal results.[1-5] Studies failed to show any measurable improvement in accident statistics after a television campaign[2] and conventional education techniques.[3] Most authors, however, are in agreement that such efforts may have longer term effects, including heightened awareness among health care workers and, perhaps, the public.[1-5]

Present measures for controlling the design and use of baby walkers are apparently inadequate in terms of safety. We suggest that further safety features be incorporated in all future models and that legislation be passed to ensure the compliance of manufacturer and supplier. In addition, a programme of public education in the use of all baby furniture and transport devices may be beneficial.

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Height at diagnosis of malignancies

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SUMMARY Studies of the presenting height of children with malignancies have produced conflicting results, from an excess of taller patients to an excess of shorter patients. The problems of measurement bias, inadequate comparison populations, small numbers of patients, subgroup analyses, and overreliance on simple significance tests are all possible reasons for the variation in results. To clarify this issue, we studied heights at diagnosis of 3657 children and adolescents aged under 18 years. Their malignancies included acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease, acute non-lymphoblastic leukaemia, osteosarcoma, retinoblastoma, neuroblastoma, Wilms' tumour, rhabdomyosarcoma, and Ewing's sarcoma. Compared with published standards for the heights of children in control populations, no significant deviation from population norms was found for patients in any of the 10 disease categories after proper adjustment for multiple significance testing.

Intrigued by Tjalma's observation of an increased risk of bone sarcoma in larger breeds of dogs,[1] Fraumeni investigated the relation between stature and malignant bone tumours in children and adolescents [2] He found that children with osteosarcoma or Ewing's sarcoma were significantly taller at diagnosis than the control group, who had non-osseous cancers, and suggested that development of these malignant tumours was related to accelerated skeletal growth. After studying 236 children with newly diagnosed acute lymphoblastic leukaemia Broomhall *et al* reported that these children were significantly taller than normal children, which implied involvement of growth hormone or somatomedin in the development of acute lymphoblastic leukaemia.[3] Hancock *et al* observed a taller stature associated with Hodgkin's disease in adults and suggested it was a constitutional factor.[4] Subsequent studies of children with osteosarcoma,[5] Ewing's sarcoma,[6] or acute lymphoblastic leukaemia[7–11] have yielded conflicting results. We studied a large number of patients with newly diagnosed malignant diseases to determine if any relation existed between unusual height and childhood malignancies.

Patients and methods

Our study included 3657 patients aged under 18 years with newly diagnosed malignancies who were admitted to St Jude Children's Research Hospital between 1962 and 1985. Patients were excluded if their heights were not measured within one month of diagnosis The 2101 boys and 1556 girls were segregated into 10 categories of disease; acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease, acute non-lymphoblastic leukaemia, osteosarcoma, retinoblastoma, neuroblastoma, Wilms' tumour, rhabdomyosarcoma, or Ewing's sarcoma (Table). There were too few patients with brain tumours referred to our centre during this period for them to be included in the analyses.

In general, standing height was used for children aged over 5 years and recumbent length for those under 5.[12] Standing height was measured with the child standing erect with closed heels, buttocks. upper part of the back, and occiput against a two metre measuring scale; the head was positioned so that the external auditory meatus and the lower border of the orbit were on a plane parallel to the floor. Recumbent length was measured with the child lying on a firm table with the soles of feet held firmly against a fixed upright placed at the zero mark; a movable upright was then brought firmly against the vertex

Heights at diagnosis of these children and adolescents were compared with normal values produced by the National Center for Health Statistics (NCHS).[13] The 5th, 10th, 25th, 50th, 75th, 90th, and 95th centile heights for boys and girls up to 18 years

Table *Standard deviation scores of presenting height of children with malignancies*

Disease		*No of patients*	*Mean of SD score*	*SE*	*p Value*
Acute lymphoblastic leukaemia	Boys	901	0·082	0·036	0·02
	Girls	690	0·043	0·042	0·30
	Total	1591	0·065	0·027	0·02
Non-Hodgkin's lymphoma	Boys	212	0·049	0·073	0·51
	Girls	83	0·254	0·108	0·02
	Total	295	0·106	0·061	0·08
Hodgkin's disease	Boys	156	−0·089	0·078	0·32
	Girls	104	0·237	0·084	0·005
	Total	260	0·048	0·058	0·41
Acute non-lymphoblastic leukaemia	Boys	242	−0·151	0·079	0·06
	Girls	186	−0·009	0·079	0·91
	Total	428	−0·089	0·056	0·12
Osteosarcoma	Boys	84	0·132	0·115	0·25
	Girls	66	0·087	0·118	0·47
	Total	150	0·112	0·083	0·18
Retinoblastoma	Boys	53	−0·408	0·273	0·14
	Girls	48	0·100	0·152	0·51
	Total	101	−0·167	0·162	0·31
Neuroblastoma	Boys	172	−0·003	0·089	0·97
	Girls	143	−0·064	0·083	0·44
	Total	315	−0·031	0·061	0·62
Wilms' tumour	Boys	105	−0·072	0·097	0·46
	Girls	106	0·030	0·107	0·78
	Total	211	−0·021	0·072	0·77
Rhabdomyosarcoma	Boys	111	−0·063	0·093	0·50
	Girls	82	0·106	0·114	0·36
	Total	193	0·009	0·072	0·90
Ewing's sarcoma	Boys	65	0·044	0·142	0·76
	Girls	43	−0·078	0·153	0·61
	Total	113	−0·008	0·104	0·94
Total	Boys	2101	0·006	0·024	0·82
	Girls	1556	0·054	0·027	0·05
	Total	3657	0·026	0·018	0·15

were obtained from cubic spline equations. These equations were produced at NCHS from charts based on data collected from 1962 to 1975.

In our study the height of each patient was converted to a standard deviation score, $(Y—\bar{X})/S$, in which Y is the patient's observed height in centimetres, $\bar{X}$ is the 50th centile of normal subjects of the same age and sex, and S is an estimate of the standard deviation of normal heights. The value of S was obtained from the cubic spline equations for a subject of specified age and sex. If a normal statistical distribution is assumed, calculating $S_\alpha^2=(X_{(1-\alpha)}-X_{0\cdot5})^2/Z_\alpha^2$, where $X_{(1-\alpha)}$ is the 100 (1-α)th centile height calculated from the NCHS equations and Z_α^2 is the $\alpha \times 100\%$ point of the normal distribution, for each centile (α=0·05, 0·10, 0·25, 0·75, 0·90, 0·95) except the 50th then six different variance estimates are yielded. The estimate (S) of the standard deviation is simply the square root of the average of the six S_α^2 values. This type of estimate is reasonable if the data are normally distributed and was necessary in this study because the sample standard deviation could not be calculated from the available NCHS data.

For each category of disease, a mean standard deviation score was computed for boys, girls, and both sexes combined (Table). A two sided *t* test was used to test whether or not the mean scores for patients in each disease-sex category were statistically different from zero.

As a result of the well known problems of multiple significance testing, some type of adjustment of the nominal p values in all of these tests was needed to avoid the spurious identification of 'significant' deviations from normality. A conservative approach is to divide the target significance level (say 0·05) by the number (k) of tests to get a level below which the nominal p value must fall to be declared significant.[14] Unfortunately, in any data sifting analysis such as this one it is difficult to identify the number of separate (but not independent) statistical tests that were actually conducted. As there were 10 categories of disease and we wished to examine the results for boys and girls separately we arbitrarily chose k=20 for a significant value—that is, an individual p value must be less than 0·05/20=0·0025 to be declared significant at the 0·05 level—even though additional tests—for example, by age—were also performed.

A more important criticism of the significance testing approach is that it fails to consider the magnitude of the observed deviation from normality. With large numbers of patients, a significant difference may be clinically unimportant and, conversely, with a small number of patients, a large and potentially important difference may be missed. Accordingly, the actual differences (in cm) for a given category are of more importance than a simple 'significant' or 'not significant' result. These data are given for the category with the smallest nominal p value.

Results

No significant difference in average height from the controls was found for any of the patients with the 10 categories of disease based on the adjusted significance level (Table) Even when the analyses were performed after further dividing patients by age—for example, above or below 1 year for neuroblastoma—no significant difference was achieved. Few of the nominal p values were below 0·05.

The single category in which the nominal significance level was close to significance was that of girls with Hodgkin's disease (nominal p value=0·005). Figure 1 depicts the distribution of heights of the patients and the median values for normal controls by age at diagnosis. There was obviously no major deviation from normality, regardless of how the p value was interpreted. Figure 2 shows the standard deviation scores of patients according to their ages at diagnosis. For example, the estimated mean (SE) increase in height for 12 year old girls with Hodgkin's disease was only 1·6 (0·7) cm.

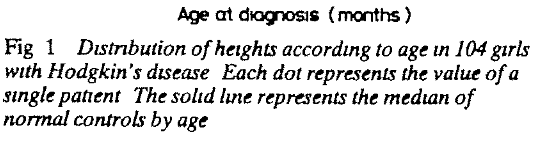

Fig 1 *Distribution of heights according to age in 104 girls with Hodgkin's disease Each dot represents the value of a single patient The solid line represents the median of normal controls by age*

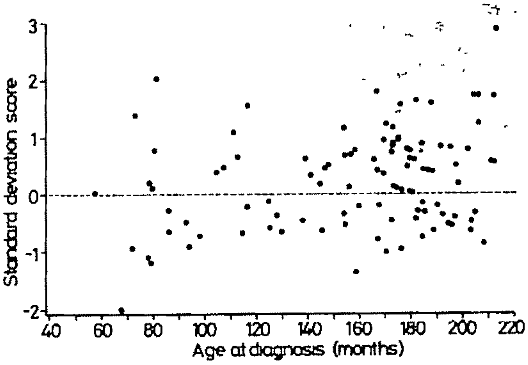

Fig 2 *Standard deviation scores according to age in 104 girls with Hodgkin's disease*

Discussion

We found no significant difference between the heights of children with malignancies and the heights of normal children in the control population. This is in agreement with the studies of McWhirter *et al*, Robison *et al*, and Bessho for acute lymphoblastic leukaemia[8–10] and that of Broström *et al* for osteosarcoma[5] Other studies have provided contradictory evidence. Broomhall *et al* found that children with acute lymphoblastic leukaemia were, on average, taller than normal controls.[3] Berry *et al*, however, reported that significantly more boys with acute lymphoblastic leukaemia aged less than 4 years, were shorter at diagnosis,[7] and Westphal *et al* found that their patients with acute lymphoblastic leukaemia were shorter and lighter.[11] Similarly, while Fraumeni reported that children with osteosarcoma or Ewing's sarcomas were taller,[2] a subsequent study by Pendergrass indicated that girls with Ewing's sarcoma were smaller.[6]

The contradictions in published results have several plausible explanations, which have nothing to do with accelerated skeletal growth, aberrations in growth hormone, or constitutional factors. The well known tendency to publish 'positive'—that is, differences are found—rather than 'negative'—that is, no differences are found—studies creates a bias toward publication of papers that confirm height differences, particularly when subgroup analyses by age, sex, and other categories are carried out. It is rare to find any adjustment to the statistical analysis caused by the multiplicity of tests carried out in a subgroup analysis. For instance, if we had used the nominal significance level of 0·05, we would have concluded that girls with any malignancy, as a group, were taller at diagnosis (Table). We could also have reported that boys with acute lymphoblastic leukaemia or girls with non-Hodgkin's lymphoma or Hodgkin's disease were taller from this study. Obviously, however, no appreciable difference in height can be observed for girls with Hodgkin's disease in this study (Fig. 1).

The reliability of the actual height measurements for the study population are rarely discussed. These studies, including the present one, are usually retrospective analyses of height data that were routinely collected, and systematic bias is always a possibility. This is especially important in a small series because the observed average height differences, even if assumed to be real, are very small in absolute magnitude.

Control populations also need careful evaluation because any deviations from the average height of healthy children of the same age, race, and sex are critical in these studies. The use of accurate published norms may seem preferable to any internal control population, but the use of internal controls measured in the same way as patients can obviate any systematic bias in measurement, even though it would be difficult to ascertain selection bias in the controls. There is no simple 'best way' to proceed, but the possibility of inadequate or improper comparisons must be considered in evaluating the publications on this topic.

Another explanation for conflicting reports is variation in the number of patients studied. For example, we were more likely to detect a small deviation from normal heights in patients with acute lymphoblastic leukaemia (n=1591) than in patients with retinoblastoma (n=101). In fact, the observed average height of boys with retinoblastoma deviated most from the average height of any normal subgroup, but it was not significant because of the small number of patients (n=53). Caution is advised with respect to any conclusion drawn from small numbers of patients in these types of studies. A rough rule of thumb is that there should be at least 100 patients in the category under study. This would permit detection with a high probability (0·90) of any deviation from normality over 0·1 standard deviation in average height and would provide reasonable precision in the estimated distribution of heights.

A cautionary note should also be made about the interpretation of results of significance testing. Overreliance on these results impedes a balanced assessment of the magnitude and precision of the observed difference and the medical importance of that difference. The significance tests normally used in these settings, even if proper adjustment for multiplicity is made, can only discriminate between the true difference and zero. Any observed difference will be declared significant if enough patients are included. An estimate of the magnitude of the differences is needed along with an estimate of its precision or standard error. For example, estimates and confidence intervals for the true height differences are more informative than simple significance tests.

Several investigators have suggested that growth hormone may influence the development and proliferation of acute lymphoblastic leukaemia.[15] Increased serum growth hormone and somatomedin concentrations were found at diagnosis of childhood acute lymphoblastic leukaemia in one study.[7] None the less any effect of growth hormone during the period of development of leukaemia seems to be clinically unimportant.

We conclude that there is no significant aberrant growth or stature associated with childhood malignancies at presentation. Future studies in this area should consider carefully the potential problems of measurement bias, inadequate comparison populations, small number of patients, subgroup analyses, and overreliance on simple significance testing.

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Twenty five years ago

A study of growth promotion in children

Douglas Hubble and Duncan R MacMillan (Birmingham)—Arch Dis Child 1962,**37**:518–24

In this study 23 children with short stature of differing aetiology were treated by methandienone in doses of 0·08 to 0·73 mg/kg/day At this time there was much interest in the new testosterone derivatives that were claimed to have a heightened effect on protein anabolism but a reduced androgenic effect As the authors pointed out these protein anabolic drugs have complicated actions that were poorly understood, so they approached their use to promote growth with a conservative attitude Their cases were placed into the following diagnostic categories, organic hypopituitarism (three cases), congenital hypopituitarism (four), Turner's syndrome (three), familial short stature (four), primordial dwarfism (five), dwarfism and obesity, mental and sexual retardation (four) All patients were given an initial course of treatment of three months' duration This was continued if there was no evidence of virilisation and no appreciable advance in bone age The presence of virilisation or of skeletal maturation proceeding faster than the rate of growth were regarded as indications for stopping treatment.

A satisfactory growth response was obtained in 10 of the 23 children, but the children in each group displayed a differing pattern of response. Six of the hypopituitary patients had a disappointing growth response and the one patient in this group who had a good response may not, in fact, have been a case of congenital hypopituitarism The authors commented that protein anabolic agents were no substitute for the growth hormone. None the less they concluded that they should be used in hypopituitarism despite their poor effect on growth promotion and that it was safe to use them when skeletal maturation is retarded (especially in late maturing boys) and in primordial dwarfs with a retarded bone age

Comment. Human growth hormone first became available in restricted amounts about the time of publication of this paper and in the ensuing 25 years has completely altered the outlook for children suffering from hypopituitarism The advent of biosynthetic growth hormone is likely to result in further pronounced changes in the treatment of retarded growth provided adequate amounts can be marketed at reasonable cost The place of anabolic steroids in the treatment of retarded growth is today even more problematical than it was in 1962 It is, indeed, very doubtful if they have any place in the treatment of children suffering from growth retardation from whatever cause

(The senior author of this paper, Douglas Hubble, was a British pioneer in paediatric endocrinology and on a par with his American counterpart Lawson Wilkins He was Chairman of the Academic Board of the British Paediatric Association from 1966–69 and James Spence Medallist in 1970 He had a remarkable command of the English language, both written and spoken, and great personal charm)

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Young doctors' views on their undergraduate child health teaching

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SUMMARY Fifty three recently qualified doctors working in various fields of child health were asked to relate their present work to the teaching they received as undergraduates. A rating scale was used that indicated the doctor's perceptions of the present importance of a subject and the previous deficiency in teaching. History taking and examination techniques were thought to have been adequately taught, but the diagnosis and management of 'minor ailments' in children were thought to have been deficient in the course, despite their importance in present work. A greater emphasis on problem based teaching would make up for this deficiency.

The relation between what is taught to the undergraduate student and the work content of the practising doctor has been studied little and there is disagreement among medical teachers about the closeness of the relation. Some teachers consider that the aim of undergraduate instruction is to educate students and provide the foundation for clinical work and that detailed training in particular skills will only come later. Others feel that the undergraduate will learn better if he or she studies the subject in a more applied way and indeed should aim at competency in some of the important medical skills.

All will probably agree that child health undergraduate teaching should emphasise those aspects of practice that are important to doctors working with children. Meadow, in his 1973 study of students' retrospective assessments of their teaching, tried to find out whether students changed their views of their course after some years in practice, but the doctors were not asked to discuss what contribution their teaching made to the child health components of their practice.[1] In the present study the aim was to relate young doctors' assessments of the child health requirements of their present work to the undergraduate teaching of the same topics or, in other words, how relevant was the course to their needs?

Subjects and methods

The method used was similar to that described in a study on the training of pharmacists.[2] It consisted of the administration of a questionnaire to recently qualified doctors working in various fields of paediatrics.

The doctors interviewed were (1) senior house officers who were in their first six months in hospital paediatrics, (2) senior house officers who were in a six month rotation as hospital casualty officers, and (3) trainee general practitioners who were in the first six months of their traineeship period (some of these had previous hospital experience in paediatrics). All the doctors were working in Tayside and represented all those who filled the above posts during the study. Twenty three senior house officers and 30 trainee general practitioners were interviewed either by the author or a research assistant.

The doctors were initially asked an open ended question 'Do you think that there are any particular areas in child health which you feel to be especially important in your present job, which were inadequately taught at your medical school?'. Each was asked to expand on this question in an informal way.

A questionnaire was then administered that related to particular content areas in child health. The topic areas were selected from a pilot study of the first 10 interviews and included topics mentioned by these doctors, with others added by the author (some because they seem to be important to a paediatrician, others as distractors). The full set of 25 topics is shown in the Appendix.

The doctors were asked to rank each topic on a scale of 1 to 5, according firstly to its importance in their present work and secondly to its deficiency or otherwise in their undergraduate teaching (A score of 1 indicated not important or deficient, a score of 5 highly important or very deficient.)

The doctors were also asked for any general comments on their undergraduate teaching and finally to rank specific recommendations on teaching on a scale of 1 to 5 (a score of 1 indicated not important, a score of 5 very important.) Details of school of qualification and postgraduate experience were obtained from each doctor

A subsample of 15 doctors were re-interviewed nine months later to determine whether increased experience affected their view of paediatric priorities.

Table 1 *Items ranked most highly for their importance in practice (all doctors)*

Examination of children—general
Examination of ears*
Handling of babies
History taking
Diagnosis of minor ailments*
Management of minor ailments*
Prescribing in children
Practical aspects of immunisation

*Received high overall ranking for deficiency

Table 2 *Items ranked most highly for their deficiency in undergraduate teaching (all doctors)*

Diagnosis of minor ailments*
Management of minor ailments*
Counselling of parents†
Management of children in trouble with police
Management of educational implications of illness†
Use of home remedies†
Health education
Role of community agencies in child health†

*Received high overall ranking for importance
†High ranking for importance from trainee general practitioners only

Results

Twenty five (47%) of the 53 doctors were Dundee graduates, 11 (21%) were graduates of other Scottish universities, and only four (8%) were graduates of English medical schools, so that our results must reflect teaching in Dundee and may not be applicable to graduates of other medical schools. Forty (75%) had graduated within the last five years (11 (20%) within two years) and were therefore likely to remember their undergraduate years in a reasonably reliable way Just over half had previous paediatric experience that might influence their judgment of the work in their present post

Table 1 ranks the top eight topics according to the doctors' views of their importance and Table 2 the top eight according to doctors' views of their deficiency. The only items that occurred in both lists were the diagnosis and management of 'minor ailments' in children. Table 1 would contain the same items if the group of general practitioners were considered separately, though the order would be slightly different, as would Table 2, with the addition of the examination of ears eighth equal.

The results of the re-interview for the items that were ranked most importantly by the whole group are shown in Table 3 In most cases there was little difference in rating at the second interview. Only the items 'time off school' and 'health education' were ranked differently in importance, while the items 'examination of ears', 'diagnosis of minor ailments', and 'time off school' were ranked differently according to their deficiency in the doctors' undergraduate teaching. The recommendations

Table 3 *Comparison of results of initial and repeat questionnaires (answered by 53 and 15 doctors, respectively)*

Item no	*Item title*	*Importance in present work*		*Deficiency in undergraduate training*	
		Initial	*Repeat*	*Initial*	*Repeat*
3	Handling of babies	4 16	4 13	3 03	2 93
4	Examination of ears	4 35	4 8	3 17*	2 47*
6	Counselling	3 36	3 8	3 77	3 87
7	Minor ailments (diagnosis)	4 47	4 66	3 5*	2 8*
8	Minor ailments (management)	4 35	4 66	3 57	3 4
10	Feeding problems	3 81	3 87	3 04	2 8
12	Prescribing	4 33	4 4	2 94	2 53
19	Time off school	3 65*	4 33*	3 51*	4 27*
20	Children and the law	2 35	2 33	4 04	4 4
22	Health education	3 58*	4 27*	3 31	3 2
23	Home remedies	3 19	3 73	3 54	4 0

Items were ranked on a scale of 1 to 5 according to their importance in current work (1=not important, 5=highly important) and deficiency in undergraduate training (1=not deficient, 5=very deficient)
*p<0 05, all other differences between ratings were not significant

Table 4 *Recommendations most highly rated by doctors*

	Recommendation	Rating group		
		Senior house officers	*Trainee general practitioners*	*Total*
1	There ought to be more emphasis on the diagnosis and management of 'minor ailments' in children	4·3	4·5	4·4
2	This would be taught best by lectures	2·6	2·5	2·5
3	This would be taught best by attachments to general practice	3·9	4·0	4·0
4	Students should be more practically involved in the ward in taking histories and examining children and have some degree of responsibility for their patients	4·3	4·3	4·3
5	In view of the number of students, this could only be achieved by a much greater use of peripheral hospitals for student attachments	3·8	3·9	3·9
6	Students should visit patients in their homes to appreciate the importance of the environment in health	3·2	3·8	3·5
7	Students should have longer attachments in the community so that they see children in a more natural environment—for example, at nursery schools and clinics	3·3	3·9	3·6
8	Students should spend more time in specialist areas, such as paediatric cardiology and paediatric neurology	2·5	2·0	2·2

Doctors were asked to rank recommendations on a scale of 1 to 5 (1=not important, 5=highly important)

Appendix

Full questionnaire and ratings by 23 senior house officers (SHO) and 30 trainee general practitioners (GP)

Item no	Item title	Importance in present work			Deficiency in undergraduate training		
		SHO	*GP*	*Total*	*SHO*	*GP*	*Total*
1	History taking in children	4·6	4·6	4·6	2·0	2·0	2·0
2	Examination of children in general	4·8	4·6	4·7	2·2	2·4	2·3
3	Handling of babies	4·0	4·2	4·1	3·2	2·8	3·0
4	Examination of ears	4·0	4·6	4·3	3·1	3·2	3·2
5	Developmental assessment in practice	3·6	3·2	3·4	2·6	2·9	2·8
6	Counselling of parents of children with chronic diseases	3·6	3·3	3·4	3·8	3·6	3·7
7	Diagnosis of 'minor illnesses'—for example, catarrh, glue ear, knock knees, rashes, crying at night	4·4	4·7	4·5	4·5	3·[illegible]	3·5
8	Management of 'minor ailments'	3·9	4·6	4·3	3·7	3·[illegible]	3·5
9	Feeding techniques in practice, including breast feeding	3·0	3·7	3·4	3·2	2·8	3·0
10	Feeding problems including colic and constipation	3·7	4·1	3·8	3·3	2·7	3·0
11	Immunisation, practical aspects	3·7	4·5	4·0	2·4	2·0	2·2
12	Prescribing in children, especially use of different formulations in practice	4·2	4·4	4·3	3·1	2·8	2·9
13	Psychiatric history taking	2·1	3·0	2·6	3·5	3·0	3·2
14	Management of behavioural problems	2·6	3·7	3·2	3·2	2·9	3·1
15	Examination of newborn	3·0	3·3	3·2	2·2	2·3	2·3
16	Management of common newborn problems	3·0	3·6	3·3	2·9	2·3	2·6
17	Management of growth and development disorders—for example, short stature	2·4	2·7	2·6	2·5	2·6	2·6
18	Management of children with handicap	2·7	3·0	2·8	2·8	2·8	2·8
19	'How long should children be off school?'	2·9	4·1	3·6	3·8	3·3	3·5
20	Children in trouble with police—procedures	2·4	2·3	2·3	4·2	3·7	4·0
21	Role of community agencies—for example, school medical service	2·4	3·4	2·9	3·2	3·3	3·2
22	Health education in practice	2·9	4·1	3·6	3·2	3·4	3·3
23	Relation of environment to health	2·7	3·6	3·2	2·6	3·0	2·8
24	Investigation of hypothyroidism	2·7	2·4	2·5	2·3	2·1	2·2
25	Use of home remedies in children	2·6	3·6	3·2	3·5	3·5	3·5

Items were ranked on a scale of 1 to 5 according to their importance in current work (1=not important, 5=highly important) and deficiency in undergraduate training (1=not deficient, 5=very deficient) most highly rated by most doctors (3·5 or over) are shown in Table 4. Almost all considered that there ought to have been more emphasis in their undergraduate teaching on the diagnosis and management of 'minor ailments' in children.

A detailed breakdown of the ratings in each area is given in the Appendix

Discussion

This study highlights certain areas of clinical practice that doctors who were entering a particular field of practice for the first time thought to be of particular importance yet that had been deficient in their undergraduate teaching. The method of obtaining the information may be criticised on the following grounds:

(1) The doctors were not sufficiently experienced to be able to assess reliably what is important in clinical practice. This may be true and it is certainly likely that additional items would be accorded greater importance by more experienced doctors. Attention must be paid, however, to the items that the doctors considered to be important for them.

(2) The doctors' memories of their undergraduate teaching may be hazy and influenced by intervening experience. Also the topic that they considered deficient may have been taught sufficiently, but they did not remember it because they were unaware of its importance at the time. It is true that certain subjects are only recognised to be important when their relevance to clinical practice is perceived. This is more a criticism of the method of teaching than of the curriculum as a whole.

(3) The doctors' prioritisation of different topics may not be consistent. Thus if they had been asked the same question on a different day a different ranking might have been given to the various items. The later interviews, which supported the earlier views of priorities, discounts this criticism.

It is pleasing that deficiencies were not noted in the undergraduate teaching of history taking and the examination of children A more objective study would be required to assess the true proficiency of doctors in these crucial areas.

Topics of considerable clinical importance, however, such as the management of common ailments in childhood, were thought by the doctors to be insufficiently emphasised in their paediatric undergraduate course. Yet as Knox pointed out, such conditions (the 'trivia' of general practice) are of considerable importance for at least three reasons: they may represent the early stages of serious disease, they are of great concern to parents, and they are often symptoms of wider family problems that require elucidation.[3] They also require specific management that may not be self evident.

Who should teach about this area, which is not easy to define as it relates more to symptoms than to diseases? Many would say general practitioners, as it is in the surgery rather than the hospital that children with these conditions are mainly seen. Logically, however, all teaching about children should be coordinated by a child health department, and to separate primary care aspects would be divisive in this era of integration. A move towards problem based teaching would help in emphasising presenting symptoms rather than diseases, and this should be encouraged. It might also be said that these topics should be taught in postgraduate rather than undergraduate education, as part of vocational training for general practitioners. It would seem important, however, for anyone dealing with children to be proficient in symptom management, and if the subject is important to a doctor this fact should be recognised in undergraduate teaching.

It must be accepted that this type of study does not provide an objective assessment of the content of undergraduate teaching as no analysis was made of the doctors' skills in the different areas. It is quite possible, for instance, that their history taking skills were inadequate but that they did not recognise this failing. A behavioural observation study would be required to provide such follow up information, which is much needed in the evaluation of undergraduate curricula.

I am grateful to Maureen Anderson, who as a research assistant carried out most of the interviews, and to the Leverhulme Trust, whose grant funded the study

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Short reports

Determinants of major handicap in post-haemorrhagic hydrocephalus

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SUMMARY The outcome of 54 low birthweight (<2500 g) infants treated by ventriculoperitoneal or ventriculoatrial shunting for post-haemorrhagic hydrocephalus over six years is reviewed. Prognosis correlated with cranial ultrasound appearances in the neonatal period but not with factors relating to the aetiology or extent or management of the hydrocephalus.

Post-haemorrhagic hydrocephalus in low birthweight infants is almost always associated with severe respiratory distress syndrome and one of its principal complications, periventricular haemorrhage. Improved survival of these infants in recent years has meant that some infants who previously died from respiratory causes now survive, but with neurological complications, such as progressive hydrocephalus. Although a number of non-surgical treatments have been advocated, only surgical diversion of cerebrospinal fluid has yet been shown to effect a permanent solution to the problem. This study examines the outcome of low birthweight infants treated by this method in a single centre and relates the findings to perinatal, ultrasound, and therapeutic factors.

Patients and methods

Between July 1979 and June 1985, 54 low birthweight infants were treated for post-haemorrhagic hydrocephalus by means of ventriculoperitoneal or ventriculoatrial diversion of cerebrospinal fluid. They represented 1·8% of all low birthweight infants admitted to this unit during that period. Most of these infants were referred either in utero or postnatally from other centres, and so this figure undoubtedly overestimates the incidence of the problem.

Cranial ultrasound scans were performed on admission, daily for the first week of life and weekly thereafter until discharge. Results were recorded as written reports together with Polaroid prints of changes seen. Early signs of periventricular haemorrhage and the occurrence during subsequent weeks of unilateral or bilateral cystic lesions of periventricular leucomalacia and porencephaly were recorded. The decision to treat an infant surgically was made on clinical grounds by one of four paediatric consultant surgeons. The ultrasound scans were available but never used as the sole criterion for surgery. Hakim low pressure, low profile ventriculoperitoneal shunts (Cordis UK Limited) were used in most infants. A few infants initially managed with ventriculoatrial shunts were subsequently revised to ventriculoperitoneal types. No particular weight had to be achieved before shunt surgery, but no infant who weighed less than 1300 g was operated on. To control the rate of head growth or symptoms attributable to hydrocephalus, intermittent spinal or ventricular needle taps were used before insertion of the shunt in most of the infants.

Data on perinatal factors, factors relating to aetiology and severity of hydrocephalus, and therapeutic interventions were recorded.

Outcome was assessed in 44 cases by regular follow up at the regional centre with a neurological examination and use of the Denver development screening test. In six children in whom distances precluded this reports from district child development centres and other consultant paediatricians were used. Specialist referral was made to the regional development centre where indicated. The duration of follow up ranged from one to six years. Follow up data were available on all survivors. As a result of the variety of sources of assessment, outcome has been graded for the purposes of this study into four broad categories. 'Normal', with no major impairments, 'Normal and cerebral palsy', with normal cognitive development but with some degree of motor impairment; 'Moderate delay (developmental quotient <80) with or without cerebral palsy'; and 'Severe delay (developmental quotient <50) with or without cerebral palsy', The significance of statistical associations was tested using Fisher's exact test.

Results

The outcomes of the infants are summarised in the Table. Of the 54 infants treated, 76% weighed less than 1500 g at birth, and 80% had a gestation of 30 weeks or less. There were four deaths, due to necrotising enterocolitis, endocarditis, pneumonia, and post-anaesthetic problems, respectively All the babies who died had a birth weight less than 1500 g. Of the survivors, 38% have required a shunt revision to date, half of these on two or more occasions.

Perinatal factors, such as gestation, birth weight, sex, place of birth, mode of delivery, Apgar scores, maternal illness or labour complications, and duration of ventilation, did not relate significantly to outcome category. Factors relating to the hydrocephalus or its management, such as maximum cerebrospinal fluid protein or pressure, occipital-frontal head circumference at operation below 10th centile, number of cerebrospinal fluid taps before operation, and age at operation also did not relate significantly to outcome.

Table *Outcome of the 50 surviving low birthweight infants (grouped according to outcome categories) with post-haemorrhagic hydrocephalus treated by ventriculoperitoneal or ventriculoatrial shunting*

	Outcome group			
	No major impairment	*DQ>80 with cerebral palsy*	*DQ 50–80 with or without cerebral palsy*	*DQ <50 with or without cerebral palsy*
n	13	11	17	9
Sex (M/F)	9/4	8/3	14/3	3/6
Median gestation (weeks)	28	30	29	28
Birthweight (g)				
Median	1246	1322	1270	1138
Range	730–2070	976–2050	910–2214	884–1310
Inborn	2	1	4	2
In utero transfer	6	3	5	3
Postnatal transfer	5	7	8	4
Days ventilated				
Median	9	11	13	14
Range	0–95	2–25	0–54	5–41
Taps				
No	7	10	11	8
Range	0–33	0–20	2–20	0–22
Age at operation (days)				
Median	80	37	48	83
Range	26–252	32–150	32–207	37–154
Fits				
None	10	5	4	0
Yes	3	6	13	9
Cysts				
None	9	3	4	0
Unilateral	3	5	7	2
Bilateral	1	3	6	7

DQ=Developmental quotient

Outcome related principally to two factors—namely, the occurrence of fits in the neonatal period ($p=0\cdot0006$) and the presence of parenchymal cysts on ultrasound scan ($p=0\cdot008$), particularly if they were bilateral in distribution. In 17% of infants clinically evident convulsions occurred before the end of the first week and in 46% between seven and 28 days. The time of occurrence did not relate to outcome, but in most cases the convulsions occurred during the period of ventricular dilatation rather than at the time of the haemorrhage. In 15 infants porencephalic cysts were first seen at a median age of 14 days (range four to 28 days) and in 21 infants small cysts of periventricular leucomalacia were seen at a median age of 18 days (range eight to 28 days) These changes preceded extensive ventricular enlargement, although they often worsened as hydrocephaly proceeded.

Four infants had severe visual impairment without retinopathy and were thought to be cortically blind. All had extensive bilateral subcortical cysts. Five other infants have less severe visual loss associated with retinopathy or optic atrophy. Two had severe bilateral hearing loss. In one of these infants hearing was normal until 18 months when shunt obstruction necessitated a revision. Three others has lesser degrees of hearing impairment but required aids.

Discussion

Although a number of small series of low birthweight infants treated surgically for post-haemorrhagic hydrocephalus have been reported in recent years,[1–5] this is the largest from one centre.

The follow up data were collected from a variety of sources but are complete and enable broad categories of outcome to be defined in terms of major impairments. It is important to note, however, that minor motor deficits and coordination problems are proving common in the older infants, even in the 'normal' category, and schooling problems are arising from these.

The finding that neonatal fits and parenchymal cysts were related to major impairment later on was not surprising as both are known as good predictors of neonatal outcome in general. Parenchymal cysts, whether of leucomalacia or porencephaly, represent cerebral atrophy occurring before extensive hydrocephaly. After shunting, however, ventricular size failed to return to normal in many infants, indicating further atrophy possibly related to hydrocephaly itself. The perinatal factors examined related to the occurrence of hydrocephalus but not obviously to its eventual outcome. Therapeutic variables, such as the age at surgery and the number of spinal or ventricular taps before shunting, did not seem to relate to later major impairment. But these treatments were determined by a number of other factors, such as the condition of the infant, rate of progression of the hydrocephalus, and changing management policies, and were not randomised Current trials may clarify the place of such management.

The strong relation of major impairment to cerebral cysts that were present before the hydrocephaly and indicated brain injury may indicate, however, that any benefit from early treatment of hydrocephalus will not be seen in a reduction in major early impairment but possibly later in the minor motor disabilities and coordination problems that characterise other forms of hydrocephalus. Follow up into primary school may be needed to detect this in such trials.

I thank Miss I Irving, Professor J Lister, Mr R Cudmore, and Mr R C M Cook for their advice and the surgical management of these babies

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Evaluation of nebulisers for bronchial challenge tests

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SUMMARY The reproducibility of the output of seven different nebulisers was tested. Nebulisers with a minimal increase in output at higher flow rates had less variability in the output. The selection of a nebuliser for bronchial provocation tests depends on the intranebuliser variability. Two nebulisers had highly reproducible outputs

Recently, bronchial challenge tests have been used increasingly for research and clinical purposes.[1] The solutions used for these tests are nebulised and administered by using either a dosimetric technique[2] or inhalations from a nebuliser for two minutes.[3] The results from the two techniques have been shown to be quantitatively similar. Many workers prefer to use the latter method ('tidal breathing' technique), because although it is more time consuming, it is much cheaper In addition, only this method is feasible in young children. Bronchial provocation tests are quantitative and therefore the administered dose must be accurate. Among the important factors determining the amount of substance inhaled is the output of the nebuliser, which must be constant throughout the test. In the present study we have determined the reproducibility of the output of seven commercially available nebulisers under standardised conditions to assess their accuracy and suitability for use in bronchial challenges.

Material and methods

A single device of seven different commercially available nebulisers was evaluated (Table). Each device was tested 10 times under identical conditions. Before and after use the nebuliser was cleaned with industrial alcohol, dried, and filled to half its maximal capacity with distilled water. The device was then put into a thermostatically controlled bath

Table *Output of nebulisers driven at the manufacturer's recommended flow rate. Each measurement was made 10 times*

	Nebuliser type						
	Wright	*Turret*	*Hudson 1720*	*Acorn*	*Inspiron*	*Hudson 1730*	*Cirrus*
Flow rate (l/min)	8	6	6	6	6	6	6
Mean (SD) [coefficient of variation] output (mg/min)	166 (6) [3.6]	313 (22) [7.0]	267 (8.5) [3.1]	326 (26) [7.9]	395 (30) [7.6]	380 (20) [5.2]	311 (21) [6.7]
Range (mg/min)	155–175	275–340	255–285	275–360	345–440	345–420	280–350

at a temperature of 26°C for 15 minutes. Subsequently, it was removed from the bath, clamped in a stand, and driven with air coming from a compressed air cylinder at a pressure of 60 psi at the manufacturer's recommended flow rate to produce an aerosol with particles of less than 5 µm in size. Flow rates were measured at the input using a rotameter. Each nebuliser was then operated for two minutes. Its output was calculated by weighing the device before and after nebulisation with an electronic balance (Sauter SD-100T) to the nearest 10 mg, and the mean of three measurements was taken as the representative 'weight'. The output of the nebulisers was also studied at flow rates between 4 and 10 l/min because of a possible relation between the reproducibility of aerosol output and flow.

Results

Inspection of the coefficient of variation of output (Table) shows that two nebulisers, the Wright and the Hudson 1720, were similar and much more reproducible than the other five. The same nebulisers also had a smaller increase in output at high flow rates (Figure).

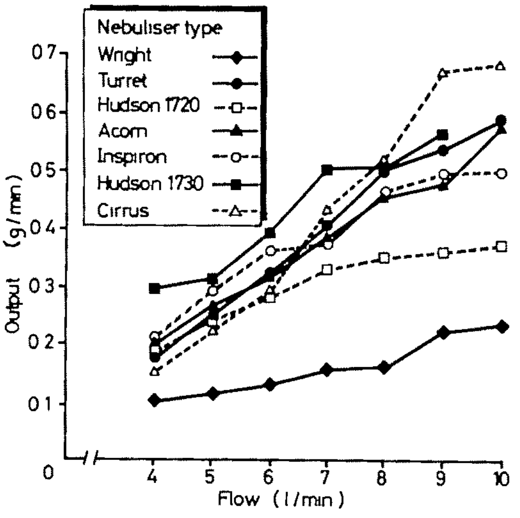

Figure *Mean output from the seven nebulisers at varying flow rates*

Discussion

Different types of commercial nebulisers are being used currently for bronchial challenge tests. We have devised a simple and easily reproduced method for evaluating nebulisers. Nebuliser output has been shown to be an important determinant of the response to bronchial provocation,[4] and a desirable nebuliser should have minimal variation in output. Output has been reported to vary not only between different types of nebulisers but also among different devices of the same type.[5] Recent reports suggest that some nebulisers are unsuitable for bronchial provocation tests because of great variation in their output.[6]

The results of the present study confirm that even if a single nebuliser is used under standardised conditions its output may vary considerably over several operations. This is not important during the administration of therapeutic solutions, where a fairly large amount of fluid is usually administered, but is critical in bronchial provocation tests, where the total administered dose is small. In this study, of the seven types of nebulisers tested, only the Wright and the Hudson 1720 had a low variation in output with repeated use. The results shown in the Table indicate that the higher the output the greater the variation. In theory smaller variations in output could be achieved by operating a nebuliser at a lower flow rate. In practice this is not feasible because lower rates of flow would result in an increase in particle size, with different airway penetration and a different clinical response.

In conclusion, before selecting a nebuliser for bronchial provocation testing there should be an awareness of the intranebuliser variability of output. Nebulisers of 'high reproducibility' should be the choice of preference for these tests

We thank Professor R D G Milner for helpful discussion

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Stunting in African children

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SUMMARY A total of 651 preschool children from rural central Africa were selected by random cluster sampling, weighed, and measured. Two per cent were wasted, but 47% were stunted. As linear growth recovers more slowly than weight repeated infections may give inadequate time for height catch up

Severe malnutrition is obvious among children in the African Sahael, and the eco-political aetiological factors are familiar and tragic. We set out to establish the nutritional state of children in more stable rural communities of subequatorial Africa.

Patients and methods

Three medical students, during their elective periods, attempted to find out the nutritional state of children in rural communities in subequatorial Africa by using small numbers but a statistically valid cluster sampling technique in rural Tanzania, Zaire, and Zambia.[1]

With local help in each area, the population was divided into 30 groups roughly equal in numbers. In each area, starting at a randomly selected point, a cluster of between seven and 10 children were selected who lived nearest and were aged between 12 and 60 months. Their weights were measured with a CMS MP25 spring balance and their heights against a scale on a vertical board with a spirit level on their heads. Birth dates were recorded.[2]

Results

Wasting was defined as less than −2 standard deviations (SD) below an international reference population (National Center for Health Statistics) for weight for height and stunting as less than −2 SD height for age (the World Health Organisation-Waterlow classification of malnutrition).[3] Of the 612

Table *Standard height for age of preschool children (aged 12–69 months) in three rural African communities*

Standard height for age	*Rural African communities*							
	Tanzania		*Zambia*		*Zaire*		*Total*	
	No	*(%)*	*No*	*(%)*	*No*	*(%)*	*No*	*(%)*
<−3	43	(19 5)	24	(11 1)	58	(28 3)	125	(20 4)
−3 to −2	61	(27 6)	59	(27 3)	58	(28 3)	178	(29 1)
−2 to −1	65	(29 4)	76	(35 2)	21	(24 9)	162	(26 5)
−1 to 0	38	(17 2)	42	(19 4)	18	(8 8)	98	(16 0)
0 to 1	11	(5·0)	10	(4 6)	16	(7 8)	37	(6 0)
1 to 2	1	(0 5)	4	(1 9)	4	(2 0)	9	(1 5)
>2	2	(0 9)	1	(0 5)	0		3	(0 5)
Total	221		216		205		612	

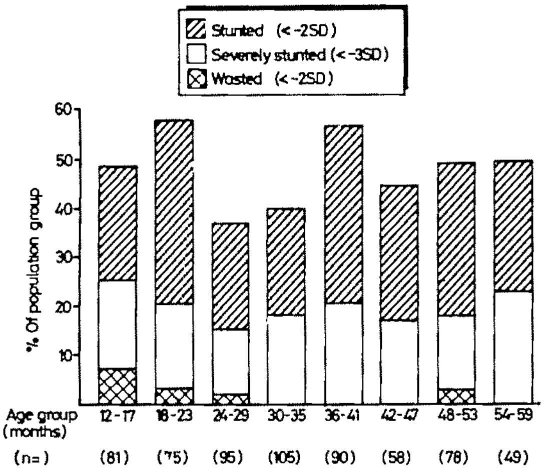

Figure *Percentages of preschool children from rural communities in Africa who were stunted, severely stunted, or wasted compared with the reference population.*

children, 1·4% were wasted, 46% stunted, and only 0·6% wasted and stunted. In this series wasting was less common than in the North American reference population. The pattern was similar in all three countries (Table) and has been reported previously.[4] Stunting was both prevalent and severe; not only were 47% less than −2 SD but 20% were less than −3 SD of height for age (Figure).

Discussion

Wasting is believed to indicate recent or current malnutrition, has correlated with increased risk of death in subsequent months, and is considered an indication for priority nutrition intervention. Stunting has not been shown to influence life expectancy and physiological function in the same way and may have a different pathological importance. When such a high proportion of children are stunted without being wasted it has to be asked if it is really an aspect of malnutrition or whether it is an adaptation to harsh environmental circumstances.

The cause as well as the importance of stunting is uncertain. Undernutrition certainly results in arrest of linear growth as well as weight loss. If prolonged undernutrition is the main cause for stunting it is surprising that there is so much of it in these populations, which have unappreciable wasting. Moreover, it might be expected that there would be a higher proportion of stunting in older age groups, but this does not seem to be the case in this rather small series (Figure).

Impaired growth during a critical period has also been blamed for shortness of final stature, and possibly the children had a low birth weight. Genetic predisposition and psychosocial deprivation are associated with stunting, and relative growth hormone deficiency may be the cause or a consequence in these circumstances. Recurrent infections with periods of arrested growth may be important in children who live in a heavily pathogen contaminated environment.

Catch up growth studied after coeliac disease may give a clue.[5] At diagnosis these children were both wasted and stunted. On an adequately nourishing gluten free diet they caught up their weight for height in three months but did not reach their expected height for age until after about 24 months of corrective treatment. Indeed, there is a period in both recovering coeliac disease and protein energy malnutrition when weight overshoots height and there is a degree of obesity.[6] A reasonable hypothesis is that in tropical Africa children catch up weight adequately after periods of growth faltering but before they have had time to fully catch up linear growth the next infection strikes. If this is the case, even with adequate nutrition, many will not achieve their full potential for height until they are protected from the pathogens in the environment. This is a further reason why the control of infections may be a major contribution to what has been considered a problem of malnutrition.

We acknowledge the help of the staff of Chavuma Hospital, Zambia, Itete Hospital, Tanzania, and Yakusu Hospital, Zaire.

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Skin rash after triple vaccine

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SUMMARY Skin rash after triple vaccine is rare. We describe a child who developed a generalised asymptomatic rash after the second and third triple vaccine. Little information of the pathogenesis of the rash is available. We argue that the development of a rash is not a contraindication to future immunisation.

Case report

A normal baby of atopic Iranian parents developed a rash five days after her second triple vaccine given with oral polio vaccine at 5 months of age. She had no systemic upset during this time. The first triple immunisation was uneventful. She was referred to the community immunisation advisory clinic by her health visitor, where she was advised to have the third triple vaccine and oral polio vaccine at the normal time. This she received at the local clinic and five days later a rash nearly identical to the first appeared. No concurrent medication was administered on either occasion. The rash was most prominent on the face (Figure), with two large macules on the trunk. The rash consisted of large ([illegible] cm) and small (3 mm) macules. Those on the trunk were slightly raised. The lesions all appeared at the same time and faded over the next four days. The child did not scratch the lesions. There were no oral lesions. Again there was no systemic upset.

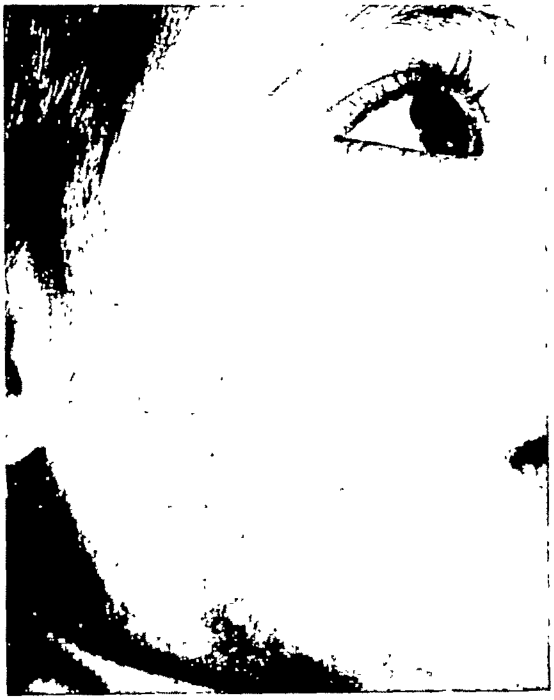

Figure *The infant's face, showing the rash, consisting of small and large macules, after administration of triple vaccine*

It was considered that the rash was probably due to the preservative thiomersal 0·01% present in triple vaccine. There have been several reports of skin hypersensitivity to this agent,[1] and one of these reports detailed delayed reactions to hyposensitisation therapy with thiomersal 0·01%. Patch testing and intradermal testing is unreliable in determining hypersensitivity.[1] In view of this, the child was challenged with 0·5 ml thiomersal 0·01% by deep subcutaneous injection. No rash occurred.

Discussion

Rash after triple vaccine does occur (Table) and is not considered a contraindication to subsequent immunisation. Of these reports to the committee on safety of medicines, some reactions are probably reported under more than one component. It is not

Table *Reports to the committee on safety of medicines of rash attributed to vaccines either in monovalent or combined forms Inclusion of a particular reaction does not necessarily mean it was caused by that vaccine*

	Tetanus	*Diphtheria*	*Pertussis*
Dermatitis			1
Exfoliative dermatitis	1	1	1
Eczema		2	10
Erythema multiforme	1	2	3
Pruritus		1	2
Rash	7	45	30
Erythematous rash	4	17	4
Follicular rash		2	
Maculopapular rash	3	9	3
Morbilliform rash		1	3
Urticaria	17	31	26
Skin discoloration	1		

Data by kind permission of the committee on safety of medicines possible to find out why some reactions are attributed to only one component and not to the normal combinations used. Furthermore, some of these individuals will have suffered viral exanthemata and some will have been treated with pharmaceutical agents, including antibiotics, which can also cause rashes. Rash is probably genuinely rare as several reports reviewing adverse reactions to vaccines do not mention rashes at all,[2] one giving an incidence of 5·2% among other adverse reactions[3] and another recording urticaria and angio-oedema occurring in 29 of 158 230 airmen, an incidence of 0·018%.[4]

Was this child's rash due to thiomersal? It has been suggested that the degradation products of thiomersal that accumulate after storage in contact lens solution cause eye hypersensitivity.[5] The accumulation of these degradation products is accelerated by storage in the light and at room temperature, but vaccines are stored in the dark and at +4°C.[5] We do not believe thiomersal was responsible for this child's rash. We also do not believe aluminium hydroxide was responsible for the rash in the light of a complete absence of reports of hypersensitivity.

The question that must be addressed is, what recommendation should be given to parents for subsequent immunisation? In the case quoted above, the question centres around diphtheria and tetanus immunisation at school entry. Both these vaccines are given to protect the individual against a potentially lethal disease, made rare by immunisation Without immunisation the child remains at considerable risk to either of these illnesses as protection wanes with time. These individuals should, therefore, be immunised if it is safe to do so. Does the five day period between immunisation and development of the rash give us any help? The rash of penicillin allergy typically occurs on the fifth day after administration and does not usually herald anaphylaxis. Perhaps the allergic mechanism involved is the same in both situations The mechanisms of penicillin allergy are, however, poorly understood. An IgE response, together with positive immediate skin hypersensitivity to tetanus toxoid immunisation, is a normal response associated with rash.[6] The IgE response has been dissected out, showing a wide range of responses, including heterogenous IgE antibody production, basophil degranulation, and basophil IgG blocking antibodies, none of which correlate with skin test positivity.[6] A report of adverse reactions to tetanus toxoid included 38 of 740 patients with generalised rash.[3] All these patients had negative intradermal skin tests and did not react to subsequent rechallenge. Even the 95 patients with previous anaphylactoid responses did not suffer any reactions to a challenge. No additional data on allergic skin reactions to diphtheria or pertussis vaccine are available.

We are left, therefore, in a rather unsatisfactory state of knowledge and can make no scientifically validated recommendations about future immunisation in those who develop a rash. We believe that subsequent immunisation will be safe in the vast majority of cases and that it is in the patient's interest to be protected against diphtheria and tetanus We advise that those immunised be observed for about an hour afterwards by a doctor to ensure that any anaphylactoid reaction that occurs is rapidly treated. We question the wisdom of continuing to use the preservative thiomersal in vaccine preparations.

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Pyloric stenosis in Western Australia, 1971–84

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SUMMARY Analyses of hospital records and census data for 1971–84 showed no significant increase in incidence of infantile hypertrophic pyloric stenosis in Western Australia. No link was found between breast feeding and incidence of disease. Low birth weight, short gestation pregnancies, and paternal family history of the disease were significant features.

The incidence of infantile hypertrophic pyloric stenosis is reportedly increasing in some areas.[1] It has been suggested that the reported increase is related to changes in breast feeding practices.[2]

The Western Australian population of 1·4 million (over 70% of whom live in Perth) is uniquely isolated geographically. The State Health Department has full coverage of all hospital morbidity and surgical procedures in the state. This allows analysis of the state wide incidence of pyloric stenosis and possible associated factors including infant feeding practices, birth weight, birth order, and sex ratio.

Patients and methods

Information about all patients in Western Australia who between 1971 and 1984 were diagnosed as having pyloric stenosis and were treated surgically was provided from the hospital morbidity collection of the State Health Department. Records of all patients who underwent operation for pyloric stenosis in Princess Margaret Hospital in the same period were examined personally by the authors.

Data were analysed using log linear models and linear regression with SPSS/PC.

Results and discussion

During the 14 year period 1971–84, 495 boys and 107 girls with pyloric stenosis were treated surgically in Princess Margaret Hospital, Perth. These 602 patients formed 97% of those with this disease operated on in Western Australia over that period.

Most features of the disease found in our cohort were typical of the established features of pyloric stenosis. These included pronounced male preponderance, clinical features, and mean age at diagnosis. The mean age at diagnosis was 5·5 weeks. The male:female ratio (4·9) was significant ($p<0·05$). The incidence per 1000 live births varied from a low of 1·4 in 1972 to a high of 2·9 in 1977 (Figure), with the male rate ranging from 1·6/1000 in 1972 to 4·5/1000 in 1978 and the female rate from 0·4/1000 in 1976 to 1/1000 in 1975. The rate varied considerably in single year periods and in 4–5 year periods from 1·7/1000 (1971–74) to 2·4/1000 (1975–79). This variation has been noted by previous workers.[1]

The slope of the regression line for the data on pyloric stenosis was not significantly different from zero, indicating that there was no significant increase in the incidence of the disease over the 14 years

Although the rate of breast feeding in Western Australia on leaving hospital increased from about 45% in 1971 to more than 80% in 1984, there was no significant difference in rates of breast feeding in infants with pyloric stenosis and in controls (Figure). Regression analysis showed the rate of change in breast feeding during the study to be significantly different from the rate of change in the disease ($p<0·05$). This finding argues against changes in infant feeding patterns influencing the frequency of this disease.

Five other features in our cohort are worthy of note:

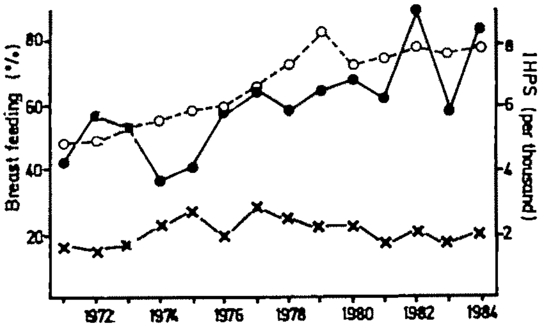

Figure *Incidence of infantile hypertrophic pyloric stenosis (IHPS) (×——×) and of breast feeding in mothers of patients with pyloric stenosis (●——●) and mothers of controls (○——○), 1971–84.*

(1) Birth order had no significant influence on the incidence of the disease in boys or girls. Birth order distribution (first born, 42·9%; second, 31·8%, third, 17·9%; fourth, or more 7·4%) did not differ significantly from census data [3]

(2) There were significantly more infants with low birth weight (<2500 g) (9·3%) in the group with pyloric stenosis than in the control population (4·9%).[4]

(3) Short gestation pregnancies (<38 weeks) occurred in 16% of mothers of patients with pyloric stenosis (excluding multiple births); this compares with 9% in the general Western Australian population. (Hitchcock NE. Unpublished data.)

(4) Several Aboriginal patients had the disease. To our knowledge, pyloric stenosis has not previously been reported in Australian Aborigines. Unfortunately, the hospital records did not describe how many of these Aboriginal patients were of full descent or were part Aboriginal.

(5) A family history of pyloric stenosis was present in 65 patients (11%), just over half being in the father's family, one quarter in the mother's family, and the rest in siblings. There were 13 multiple births involved. In only two instances were both infants affected, and in one set of all male triplets only one infant was affected. Pyloric stenosis has been shown, in other studies, to be significantly more common in children of affected parents, especially if the affected parent is the mother[5 6]—perhaps because the gene responsible for the disease in girls has greater penetrance than that responsible for the disease in boys. This was not our experience in Perth.

We are grateful to the medical records staff of Princess Margaret Hospital for their cooperation and to the Health Department of Western Australia and the Australian Bureau of Statistics for statistical information.

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Pulmonary haemosiderosis and gluten

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SUMMARY A child with idiopathic pulmonary haemosiderosis for three years required three monthly transfusions. Circulating avian, gliadin, and reticulin antibodies suggested the diagnosis of gluten enteropathy, and jejunal biopsy showed subtotal villous atrophy. During 15 months on a gluten free diet his growth and behaviour improved and he required no transfusions.

Pulmonary haemosiderosis is characterised by recurrent pulmonary infiltrates due to alveolar haemorrhage, anaemia, and finding haemosiderin laden macrophages in the sputum. In adults certain systemic disorders may be associated, but in children no specific cause is usually found. A proportion, however, have circulating antibodies to cow's milk proteins, and withdrawal of cow's milk from the diet may be beneficial.[1]

Case report

The boy was born at term weighing 2490 g and was formula fed. At 2 years of age his height and weight lay just below the 3rd centile.

He presented aged 4·5 years with a few days' history of pallor and decline in his chronically poor appetite. His height (1·06 m) and weight (15·5 kg) still lay just below the 3rd centile. An initial haemoglobin concentration of 5·2 g/dl was attributed to iron deficiency, but an erythrocyte sedimentation rate of 50 mm Hg in the first hour was not explained. He was re-admitted three days later with a haemoglobin concentration of 3·9 g/dl, a cough, scattered crepitations, mild eczema, small cervical lymph nodes, and a palpable spleen tip. Investigations showed 5% reticulocytes; iron 3 μmol/l, and total iron binding capacity 81 μmol/l, a Coombs' test yielded negative results, and stools were occult blood positive three times. He was thought initially to have cardiac failure but a chest *x* ray film showed unexpected bilateral pulmonary infiltrates, which ultimately led to the diagnosis of idiopathic pulmonary haemosiderosis. He was transfused and the lung signs and chest *x* ray film cleared in four weeks.

Over the next 30 months he had 10 similar episodes of cough and pallor associated with infiltrates on his chest *x* ray film. These no longer cleared completely between episodes and showed an increasing profusion of micronodular shadows. He required repeated blood transfusions (Figure) His height continued parallel to the 3rd centile but his weight fell away slightly. Inhaled disodium cromoglycate for three months had no effect.[2]

Re-investigation at 7 years gave similar haematological results and folate, vitamin B_{12}, albumin, globulin, zinc, IgG, IgM, IgE, and complement concentrations were normal. No abnormal circulatory autoantibodies were detected; in particular, antiglomerular basement membrane antibody was not found Other investigations are shown in the Table. Macrophages laden with haemosiderin were present in gastric washings. Radioallergosorbent tests against aspergillus, cladosporium, and cow's milk yielded negative results and skin prick tests showed +++ to house dust mite and + to mixed feathers only. IgG precipitins were present against pigeon serum, budgerigar serum, chicken serum, and egg yolk but not against milk proteins. This pattern of precipitins was not that associated with bird fancier's lung; it was, however, typical of the pattern reported in coeliac disease.[3] Gliadin antibodies (+++) were present, jejunal biopsy examination showed subtotal villous atrophy, and a gluten free diet was therefore begun

Over the subsequent 15 months his weight and height velocities have increased modestly and from

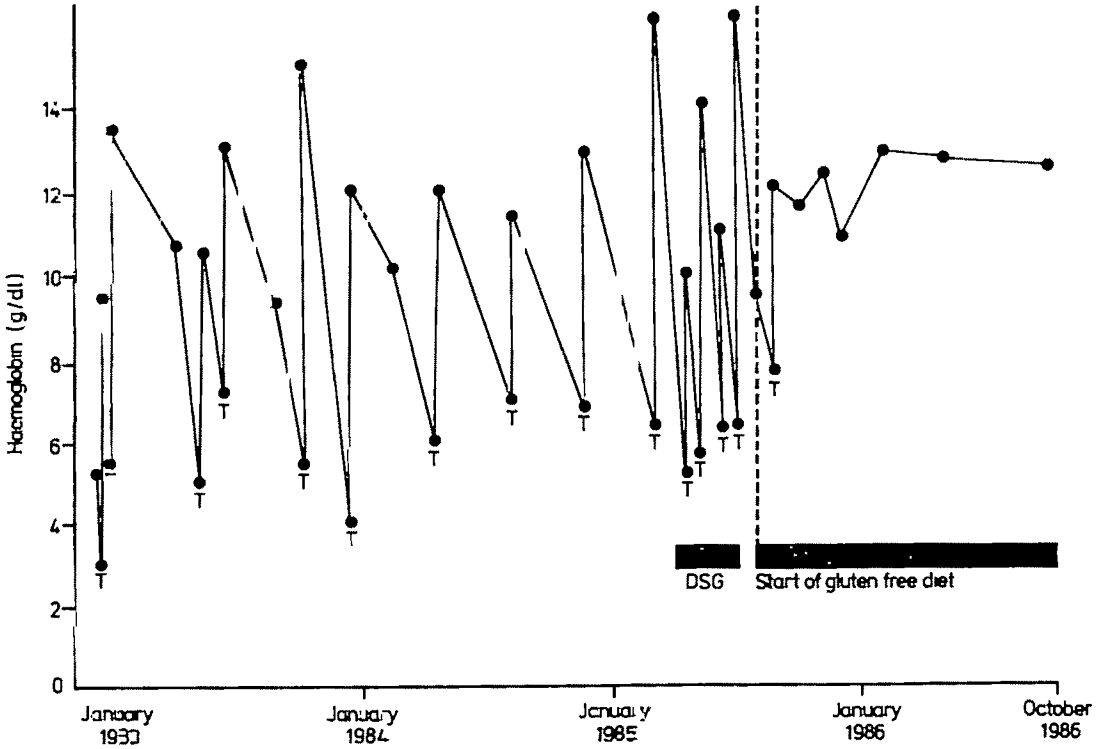

Figure *Haemoglobin concentrations over three years in a case of idiopathic pulmonary haemosiderosis who required transfusions (T) every three months until he was put on treatment with a gluten free diet An unsuccessful trial with disodium cromoglycate (DSG) is also shown.*

Table *Results of investigations before and seven months after starting gluten free diet*

	Before starting diet	*Seven months after starting diet*	*Normal range/ reference values*
Iron (µmol/l)	9	21	13–32
Total iron binding capacity (µmol/l)	68	46	43–73
Immunoglobulin A(g/l)	3·3	0·81	0·5–2·3
Reticulin antibody	1/80	Negative	Negative
Precipitins to			
Chicken serum	++	−	
Budgerigar serum	++	−	
Pigeon serum	+	±	
Egg yolk	++	−	
Forced expiratory volume in one second/ forced vital capacity	0·6/0·6	0·79/0·87	0·95/1·25

one month after starting his diet he has required no further transfusions (Figure) Re-investigation after seven months showed a haemoglobin concentration of 12·6 g/dl, with 1% reticulocytes. The results of other investigations are shown in the Table. Chest *x* ray film showed unchanged widespread micronodular shadowing. Jejunal biopsy examination showed mildly stunted villi with some epithelial stratification and an increased epithelial lymphocyte count. Gliadin antibodies remain strongly positive.

Discussion

Reports of an association between pulmonary haemosiderosis and villous atrophy are uncommon, with no previous report of gluten withdrawal leading to an improvement in the pulmonary disorder Three single case reports document a young adult with pulmonary haemosiderosis who had coeliac disease in childhood,[1] a young adult with coincident pulmonary haemosiderosis and coeliac disease,[4] and an 18 year old with a probable 11 year history of both conditions.[5] The only reported series is of seven young adults with pulmonary haemosiderosis who underwent jejunal biopsy examination. Only three, of whom only one had bowel symptoms, had any villous atrophy.[6] Although treated with a gluten free diet, no follow up data were presented.

Pulmonary haemosiderosis has not been reported previously in association with antibodies against food antigens other than milk proteins. Our patient is unusual in having antibodies against gliadin and egg yolk but not against milk. We believe this to be the first report of clinical features of pulmonary haemorrhage responding dramatically to a gluten free diet.

The response of the chronic blood loss to a gluten free diet suggests this association is not coincidental but is secondary to the gluten enteropathy. Another possibility would be a common primary defect, but the response of both conditions to the diet does not support this. Furthermore, there was no clinical or serological evidence of autoimmune disease

A reasonable suggestion is that dietary antigen, probably gluten, caused the villous atrophy, leading to antigen penetration and systemic immunisation, resulting in IgG antibodies and subsequent formation of immune complexes. Pulmonary damage would follow their deposition in the lung and demonstration of tissue fixed immune complexes would have supported this theory had a lung biopsy examination been undertaken

Although the second biopsy examination did not yield entirely normal results, we think the clinical and histological response to a gluten free diet was sufficient provisionally to diagnose gluten enteropathy. In view of the severity of his previous symptoms, gluten challenge may be contraindicated. Whether withdrawal of other dietary antigens would cause further improvement in his growth and villous architecture and the use of steroids for his pulmonary haemosiderosis are speculative.

We suggest that all children with idiopathic pulmonary haemosiderosis should undergo an intestinal biopsy examination. Gliadin antibody and precipitins to other food antigens should be measured at intervals. There is no prima facie reason why milk should contain the only food antigens associated with pulmonary haemosiderosis

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Intracranial pressure estimation by palpation of the anterior fontanelle

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SUMMARY Simultaneous assessment of intracranial pressure by anterior fontanelle palpation and direct measurement from a cerebrospinal fluid cannula showed that mean pressure was significantly different between 'soft' (5·4 mm Hg) and 'tense' (14·0 mm Hg) fontanelles, but with considerable overlap. Normal fontanelle tone was often confirmed, whereas clinical assessment of raised intracranial pressure was unreliable.

Measurement of intracranial pressure is of great importance in the neonatal period because of the number of conditions in which it may be raised, the possible consequences of its rise, and the efficacy of modern methods of treatment. Conventionally, intracranial pressure is assessed by palpating the anterior fontanelle with the finger.[1 2] The rationale is that the bony defect of the anterior fontanelle acts as a pressure vent, displaced centrifugally by an increase in intracranial pressure.

In comparison with invasive measurements of intracranial pressure in the newborn, fontanelle palpation has the advantages of being simple to perform, cheap, and free from adverse effects. Its only disadvantage is the inevitably intermittent nature of the assessment. Despite claims of its reliability,[3] there are no published reports comparing actual intracranial pressure and results obtained by clinical assessment.

Patients and methods

During the study of intracranial pressure in normal and abnormal neonates, 17 babies in our neonatal unit underwent invasive measurement of intracranial pressure at the time of clinically indicated removal of cerebrospinal fluid (CSF). Their gestational ages ranged from 24 to 41 weeks. The intracranial pressure was measured precisely by a Gaeltec pressure transducer (Gaeltec Ltd, Dunvegan, Isle of Skye, Scotland) coupled to a Tektronix monitor (Tektronix Inc PO Box 500, Beaverton, Oregon 97077, United States), which was connected by a short length of non-compliant tubing to a CSF cannula (a 23 gauge butterfly or 22G spinal needle) placed in the lumbar subarachnoid space or lateral cerebral ventricles as clinically indicated.[4] Care was taken to establish the presence of craniospinal communication for lumbar pressures.[4] Pressure was recorded when the baby was at rest in a lateral horizontal posture and referred to the level of the right atrium.

The anterior fontanelles of the babies were palpated by one of us (AMK) before the precise measurement on 59 occasions, while the baby was horizontal and at rest. At the time of measurement, the babies' postmenstrual ages varied from 28 to 80 weeks and chronological ages from 1 day to 53 weeks. All fontanelles were at least double the area of the fingertip, so the difficulties commonly encountered in assessment of small fontanelles did not occur. The fontanelle tension was subjectively classified as 'soft', 'full', or 'tense', according to the resistance to gentle digital pressure.

The distribution of precise measurements of pressure between each fontanelle tension group was compared by Student's unrelated *t* test.

Results

The fontanelle tension was classified as soft on 31 occasions, full on 14, and tense on 14.

The distributions of invasive measurements were skew to the right, so they were converted to Gaussian by taking logarithms to base 10 (Figure). Analysis was performed after this transformation, so the range is described as mean (2 standard deviations) to overcome the difficulty of describing log results. The means (ranges) were 5·4 (1·9–15·7) mm Hg for the soft group, 8·8 (2·6–30·2) mm Hg for the full group, and 14·0 (3·3–59·3) mm Hg for the tense group. The means differed at the 0·1% level for the soft and tense groups and at the 2% level for the soft and full groups, the full and tense groups were not significantly different.

There was considerable overlap between the groups. For example, 9·7% of all the pressures recorded in the soft group were >10 mm Hg, commonly taken to be the level of pressure at which intervention is indicated.[5] Conversely, 50% of all those in the tense group were <10 mm Hg

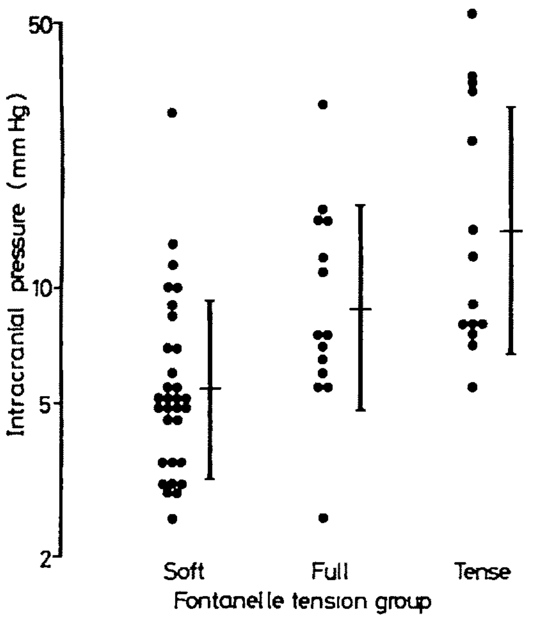

Figure *Intracranial pressure (logarithmic scale) in babies with soft, full, or tense anterior fontanelles The horizontal bar represents the mean and the vertical bar one standard deviation*

Discussion

We have shown that there is some agreement between the precise intracranial pressure value and its assessment by palpation, in so far as there was a significantly different distribution of pressures between the soft and tense and between the soft and full fontanelle tension groups. The clinical usefulness is limited, however, by the broad overlap between the distributions, even if the intermediate full group is ignored. This overlap would have led to the incorrect management of 9·7% of the soft fontanelle group and 50% of the tense fontanelle group, which altogether comprised 22% of the sample in those two groups.

No greater accuracy of digital assessment was found even when one baby was assessed over the course of time. Thus the variability was not only limited to the group as a whole but also to individual babies. This was not related to the gestational, chronological, or postmenstrual ages of the subjects.

The most likely reasons for the unreliability in palpation of fontanelle tension are the variability of skin hydration and of the compliance of the scalp and dura between babies and at different times in the same baby.

These findings suggest that it is not safe to rely on the digital assessment of fontanelle tension when treatment of raised intracranial pressure is under consideration. On the other hand, in the group considered clinically unequivocally normal, about 90% of the invasive measurements were at an acceptable level.

Mr J Messeguer maintained the electronic equipment The nurses on the neonatal unit helped in the performance of pressure measurements AMK was supported by Birthright

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Personal practice

Liaison psychotherapy in a hospital paediatric diabetic clinic

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SUMMARY A psychotherapist joined the medical team of the paediatric diabetic clinic three years ago. After some initial difficulties all agreed there had been appreciable benefits, not only to individual patients but also to the team in their handling of the psychological aspects of diabetes.

The relation between the psychological and physiological state of children with diabetes has been recognised for many years.[1-3] Various studies have investigated aspects of juvenile diabetes, nearly all using a linear hypothesis of cause and effect, such as the association observed between poor diabetic control and the emotional tone at home.[4] Development of the application of general systems theory emphasised the role of feedback mechanisms.[5] Minuchin proposed a tentative model to account for the structure and functioning of a family with a child with poorly controlled diabetes.[6-8] This holds that three factors in conjunction are necessary for the development of appreciable psychosomatic illness in children

(1) The child is physiologically vulnerable, in this case, already has diabetes.

(2) The child's family has characteristics of overprotectiveness, rigidity, and lack of conflict resolution.

(3) The sick child plays an important role in the family pattern of conflict resolution; the symptoms in turn are reinforced by that role.

Despite widespread acceptance that family assessment and family treatment are helpful in the management of psychosomatic problems,[9] such skills are not currently part of most physicians' therapeutic repertoire.[10] Laron *et al* concluded that psychological stability is a basic factor in the control of juvenile diabetes and advocated a multidisciplinary approach to its treatment.[11] At the Israel Counselling Centre for Juvenile Diabetes, in addition to a medical review, counselling by either a psychologist or a social worker at each visit was shown over 10 years to have a beneficial effect on the child's diabetic control.

Setting up the liaison

Three years' experience of regular incorporation of psychotherapy skills within the paediatric diabetic clinic in Cambridge are described. The team consisted of one consultant, two part time paediatric senior registrars with a long term commitment to the clinic, and a paediatric registrar who joined the clinic for the two years of his appointment. There was a regular dietitian and a specialist nurse who worked solely with people with diabetes, both adults and children. A health service psychotherapist (JDJ) was approached by the specialist nurse to join the team. A meeting with all members of the team was then arranged and the psychotherapist joined the team at the weekly clinic in 1982.

In this area the child with diabetes was usually admitted to the paediatric ward for a few days at the time of diagnosis. The psychotherapist introduced herself as a member of the team. She only felt comfortable thus introducing herself once she was accepted as a member of the team. This required understanding the unstated rules by which the professional system functions; attempts to alter the structure and functioning of families are ineffective if the therapist has not properly joined the professional 'family'.

Liaison role

At each clinic the psychotherapist sat in with one of the doctors or the nurse. Occasionally, a child, or more often his mother, asked to see the 'psychiatrist'. At the end of each clinic there was a team discussion about all the patients. Originally, patients were seen by the doctors in their order of arrival at the clinic. With a small number of attending doctors it was thought sensible for the child and his family to know all the members of the team. As a member of the professional 'family' the psychotherapist appreciated the physician's concerns but as a therapist she witnessed counterproductive confusion in the child and family exposed to different medical approaches. As a result, practice within the clinic was changed, ensuring increased continuity of medical care for the more psychologically vulnerable children. Dependence of children on an individual doctor was recognised and the beneficial aspects of such dependence better utilised.

Case report. An illustrative example is that of a 12 year old girl who had had diabetes for a year. She was a rebellious, surly child with erratic diabetic control. Since diagnosis she had had one admission to hospital in hypoglycaemic coma. She had one younger brother. Her father was on shift work. At the clinic her mother often looked worried and seemed unable to make clear to her daughter what she expected—for example, regular blood or urine tests, regular mealtimes, etc. After an early interview with the whole family, during which the psychotherapist tried (not very successfully) to enable the father to be more involved, her diabetic control improved a little. She saw a different paediatrician, a locum, in the summer preceding her move from junior school to a large comprehensive school. The change of doctor probably meant that an important life cycle event was missed. Neither the patient nor her mother was able to deal satisfactorily with the new school and the move coincided with another period of poor diabetic control. In retrospect, seeing the same paediatrician and being aware of life cycle changes would have been helpful to her.

Problems within the professional team

At times there are boundary and hierarchical difficulties within the professional system. In this clinic the constant professional was the diabetic nurse, who had considerable knowledge of the child's family and home life. Patients quickly worked out which problems to bring to the doctor and which to the nurse. Sometimes the offerings to each were very different; then confusion and occasionally disagreement arose between the doctors and the nurse. Sometimes outside agencies involved with the family became embroiled in dispute with a member of the clinic. The following case illustrates such a problem.

Case report. A 15 year old girl with diabetes lived at home with her mother, stepfather, and two siblings. She was seen towards the end of the clinic to avoid missing much school The doctors in the clinic found her mother difficult and unwilling or unable to understand the principles of diabetic management. The patient's mother and stepfather had a poor relationship and quarrelled. The paediatrician concerned was surprised one afternoon to be handed a letter by the patient from her general practitioner in which he wondered why she had to come to the clinic so early and miss a whole afternoon's school. At a meeting between the clinic team and the general practitioner the psychotherapist pointed out the ways in which the professionals' disagreement seemed to mirror the disagreements of the family. The general practitioner and the paediatricians were enabled by their understanding to stop 'quarrelling'.[12]

Adolescents

Erratic diabetic control in adolescents is a well recognised problem.[13–15] Some families with adolescents who have such 'brittle' diabetes conform to the characteristics described by Minuchin, but some do not. At this stage in the life cycle greater independence is encouraged, separation from the family starts, and a degree of non-conformity is expected. It is at this point that diabetes seems to make unreasonable demands. It is necessary to consider both the internal world of the adolescent with diabetes (with the problem posed to self esteem, independence, sexuality, and the idea of being 'damaged') and the relational aspects of these problems within the family. Adolescents with difficult diabetes present a serious challenge to their paediatricians. Indeed, there are uncertainties at times about who is in control. There is a paradox in suggesting increased outpatient visits at the same time as encouraging independence in their diabetic care.

Case reports.

Case 1

The patient developed diabetes when she was 11 years old and her control was reasonably good for a year. The onset of puberty coincided with her older sister being sent away from home for flouting the family's code of acceptable sexual behaviour. No attempt was made within the family to resolve this conflict Her diabetic control deteriorated and she caused her family and the paediatrician anxiety and anger by omitting injections and diet breaking.

She was admitted at 14 years because of poor control. The paediatrician knew something of the patient s family, the main observation being that her mother was overinvolved and 'hysterical'. Little was known about the rest of the family except that her older sister was not living at home. There was a sense of crisis to which the psychotherapist responded by immediate intervention with the family while she was an inpatient. The paediatrician concerned was unable to be present at the initial interview. As a result, the purpose of the meeting was not clear to the family. Further discussions with the psychotherapist were resisted but restarted at the next crisis three months later.

In the course of intensive work with the patient, her parents, and sister the overinvolvement within this family was revealed by the father saying of the mother 'we are like one person sitting on two seats' As a result of psychotherapeutic intervention the patient began to feel better and her weight increased from the 10th to the 75th centile in proportion to her height. The family did not feel comfortable changing so fast. They avoided further involvement by transferring themselves to another paediatric clinic.

Although a time of crisis can be a good point for a psychotherapist to intervene, it can be counterproductive to intervene too hastily. There is a fine line between using the crisis to enable change and mobilising family resistance by acting too quickly.

This case also illustrates the importance of discussion beforehand between the paediatrician and the psychotherapist.

Case 2

In spite of longstanding difficulties with diabetic control at transition points in the life cycle the psychotherapist may only become involved at adolescence.

An example of this is a 16 year old who had had diabetes since 5 years of age. When she was 8 years old her parents divorced and she and her younger sister lived with their father. Her diabetes was well controlled. Both girls then went to live with mother when the patient was 10. Her diabetes became unstable with rising glycosylated haemoglobin values and falling growth velocity. The paediatricians had always seen her as vulnerable to the stresses in her family, her poor growth, associated with unstable diabetes, being in part a reflection of those stresses. Despite having made that assessment, family meetings only occurred after an admission to hospital at the age of 16.

The paediatrician concerned set up a meeting in normal clinic time with the patient, her mother and sister, and the psychotherapist. Prepared by discussion about her poorly controlled diabetes and the role of the family dynamics, the psychotherapist was introduced in a way that enabled her to be effective. It seemed important that it was the paediatrician who had convened the meeting. During several further meetings with the family the psychotherapist and paediatrician enabled them to get on better together and improve their communication. It was then no longer necessary for the patient to use her unstable diabetes as a tool to control her family. Despite some minor setbacks, progress was maintained and on transfer to the adult clinic her height and weight had improved from the 10th to the 25th centile and she had a stable glycosylated haemoglobin concentration of 9·4%.

Case 3

Individual involvement with the psychotherapist in reference to a specific issue may be helpful.

A 13 year old boy had had diabetes for a year. His mother was anxious about his withdrawn manner and his preoccupation with death from diabetes. His glycaemic control was excellent and he seemed to have learnt the practicalities of diabetic management well. A meeting was arranged with the psychotherapist at which a family tree was drawn and the inter-relationships between family members clarified diagrammatically.

The patient seemed to be overprotected by his mother but unsupported by his father. Each worried about the other. After some discussion it was decided that he would be allowed to exert his own independence by organising his own snacks. In this small way he could begin his separation from his mother. A few weeks later this had been achieved The boy was more talkative and less preoccupied with death, and the level of family anxiety was reduced. Focusing on the relational aspects of his problem allowed resolution of his internal worry.

The use of family trees

As in most clinics, the whole family is rarely seen except at times of crisis. Much family information is available but its therapeutic use is not always clear to the paediatric team. There is some reluctance in using family trees despite evidence of their usefulness. Liebermann suggested that this reluctance may arise from uncertainty in the handling of information presented by geneogram.[16] This usefulness is illustrated by the following cases.

Case reports.

Case 1

A newly diagnosed 8 year old girl was the oldest of three children. Her mother was sure that her daughter would die from diabetes like her own aunt. The mother's first cousin also died in a diabetic coma in his twenties, within the last few years. A knowledge of the family history made the mother's guilt and anxiety easier to understand and reduce. The question 'In what ways is your daughter different from your aunt and cousin?' turned out to be helpful. After a couple of outpatient visits the mother no longer mentioned the deaths in her family, but it can only add to the paediatrician's skills to be aware of this child's family history.

Case 2

A copy of the family tree (Figure) has now been put in front of the patient's case notes. The psychotherapist was asked by one of the paediatricians to see the boy, aged 9 years, who had been admitted in ketoacidotic coma. After a change in insulin regimen he was physically well but continually complained of feeling sick. The psychotherapist drew a family tree with him and his mother as a way of getting to know the family. As can be seen from the diagram, the family was complicated. The child's parents were divorced, he and his younger sister living with his mother and stepfather, plus two of the stepfather's sons, both of whom were a lot older than him. There were two sets of grandparents and one set of stepgrandparents. In talking about the family two important factors emerged—the child's rivalry for his mother's attention with his older stepbrothers and his anxiety about his stepfather's mother, who was ill in hospital. With the aid of the family tree his mother understood her son's problems and was able to reassure him more clearly. As a result of this short interview he was no longer sick and left hospital, and the beneficial changes have been maintained. The patient is now a lively 10 year old coping well with his diabetes within his family.

Discussion

A number of issues are raised by the inclusion of a psychotherapist within a paediatric team. The benefit to individual patients of such liaison is shown in the examples quoted. A more general effect was felt by the whole team in their handling of the psychological aspects of juvenile diabetes. Learning to place diabetes in the context of the family's life cycle allows a broader therapeutic approach, with attention to the whole family. Greater success is achieved, however, when there is paediatric concensus that family treatment may be helpful and when it is actively supported by the whole team.

Achieving professional collaboration is not always easy. There was initial apprehension on both sides. As in all mixed marriages it takes time and effort to make the marriage work! Collaboration can only work if there is a long term commitment on both sides. Change in any organisation is slow and to expect quick results inevitably leads to disappointment. The mutual frustration can then move to a symmetrical escalation with each partner, overtly and covertly, accusing the other of being unhelpful or slow to change. This type of escalation is more likely if the paediatrician and psychotherapist are competitive and not truly cooperative. Both partners must respect each other's therapeutic boundaries. A knowledge of the disease makes the psychotherapist more credible to both the paediatrician and the patient.

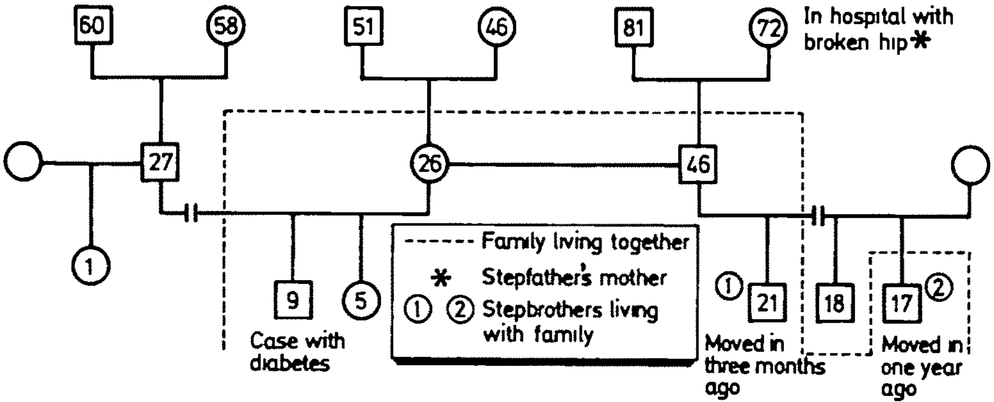
60
58
51
46
81
72
In hospital with broken hip*
27
26
46
1
9
5
Case with diabetes
------ Family living together
* Stepfather's mother
① ② Stepbrothers living with family
①
21
18
17
②
Moved in three months ago
Moved in one year ago

Figure *Family tree of case 2*

The following questions have to be addressed at some level for the liaison to be successful. What are the agendas of the various professionals and what are their secret agendas? Does the psychotherapist want to teach the paediatricians about emotional development, family treatment and psychiatric illness? Does the paediatrician wish to be relieved of difficult emotional problems by the psychotherapist? Paediatricians and psychotherapists tend to employ different conceptual frameworks, which can lead to mutual misunderstanding if not frank disagreement. Traditional medical training espouses a linear model of aetiology and appropriate treatment. A systems model, however, involves circular causal loops, such that a child's poor diabetic control, for example, affects and is affected by the family. Liaison can only be effective once the different approaches are understood.

The psychotherapist needs to be sensitive to the different abilities and wishes of the paediatricians and nurses in involving themselves in the emotional turmoils of their patients. The skill comes with learning when to press on and when to hold back. In our opinion it is the observation and comment on the therapeutic system from within that makes liaison effective. Such a system could probably be applied advantageously to the follow up of children with chronic diseases.

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Current topic

Molecular abnormalities of collagen in human disease

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Collagen proteins are a diverse family of structural materials serving a mechanical supportive role in widely varied tissues such as skin, bone, muscle, blood vessels, cartilage, pleuroperitoneal linings, hollow tubular organs, tendons, heart valves, and basement membranes. They may also possess a crucial directive role in embryogenesis and fetal development. The molecules are large, ranging between 50 and 200 Kd. There is ample scope for major mutations, which produce a diverse group of multisystem diseases relevant to all medical specialities. Type I collagen mutations have been implicated in hereditary brittle bone disease, which ranges in severity from a mild premature osteoporosis to lethal childhood dwarfism Type III collagen mutations occur with Ehlers-Danlos syndrome type IV and related disorders and present with arterial rupture (of large and medium sized arteries), intestinal diverticula, and mitral valve prolapse.

Recent spectacular advances in molecular biology, particularly with recombinant deoxyribonucleic acid (DNA) techniques such as gene cloning, restriction enzyme cleavage of DNA molecules, DNA sequencing, and DNA transfer (by microinjection) into other animal cells, in principle allow the precise dissection and analysis of any mammalian gene.[1-3] Even if the gene is unidentified, random DNA sequence variations occur sufficiently close to the disease locus to be used as predictive linkage markers in genetic pedigree analysis of both autosomal dominant and recessive diseases. Such an approach has been brilliantly successful in the molecular dissection and prenatal diagnosis and prevention of the various α and β thalassaemias,[2] has allowed accurate predictive diagnosis of Huntington's chorea,[4] and most recently has identified several markers close to the cystic fibrosis gene.[5 6]

McKusick lists over 3000 single human gene disorders,[7] and certainly we can expect a golden era for the accurate scientific diagnosis and analysis of a substantial number of single gene human diseases as well as the molecular unravelling of the various disorders of growth and development and the closely related mechanisms for carcinogenesis and disordered growth. Collagen structural genes are now all amenable to molecular analysis of this type and in the next few years we can expect that all the relevant structural genes and proteins will become cloned, sequenced, and located to specific chromosomes. Already the human genes for $\alpha1(\mathrm{I})$, $\alpha2(\mathrm{I})$, $\alpha1(\mathrm{II})$, $\alpha1(\mathrm{III})$, $\alpha1(\mathrm{IV})$, $\alpha1(\mathrm{V})$, $\alpha1(\mathrm{IX})$, and $\alpha1(\mathrm{X})$[8-15] have been at least partially cloned and sequenced and others may be expected to follow rapidly. Various diseases of collagen proteins, including osteogenesis imperfecta, Ehlers-Danlos syndrome types I, II, III, IV, and VII. Marfan's syndrome, dystrophic epidermolysis bullosa, congenital aneurysms of the circle of Willis, some types of osteoporosis, osteoarthritis, and probably some forms of congenital heart disease can increasingly commonly be expected to show specific collagen gene and protein mutations. Using a combination of fibroblast cultures from 2–4 mm punch biopsy specimens, leucocyte enrichment from blood samples supplemented occasionally with cartilage, endothelial, and keratinocyte culture, most or all of them may be expected to have specifically identified gene defects in the near future. As such they will then be preventable in principle and in practice.

Collagen genes and proteins

Ten main collagen types have been identified so far and more are likely. The most common and widespread are the so called interstitial collagens, such as types I, II, III, and probably type V proteins,[16] which share a tightly coiled triple helical central portion with N and C globular extensions and assemble into cross banded fibres. These substances are widely distributed in bones, skin, tendon, blood vessels, and cartilage. Other atypical proteins with globular elements interspersed along the collagen helix have also been identified. Type IV[17] is a good example, consisting of at least two protein chains, which form the main collagenous components of the lamina densa of basement membrane Types VI,[18] VII,[19] VIII,[20] IX, and X[15] collagens are fairly minor components of arterial basement membrane, anchoring fibrils and epiphyseal cartilages, respectively.

Type I collagen is a heteropolymer with two genetically distinct component α chains forming substantial proportions of skin, bones, arteries, tendons, and the gastrointestinal tract. Type II collagen occurs only in articular cartilage, and type III collagen is the main collagenous component of arteries, veins, and pleuroperitoneal linings (although it can also be detected in skin, gastrointestinal tract, and heart valves). Type IV collagen is widely distributed in the basement membranes of skin, lungs, gastrointestinal tract, kidneys, and blood vessels

The interstitial collagens (I, II, III, and V) are enclosed by large genes, which range from 28–40 Kb, with 50 intervening sequence (introns), 5 Kb of coding sequence (exons), and substantial homology at the 3' (C terminal) and 5' (N terminal) ends[8–11] The precursor procollagens of 120 Kd are subsequently processed into the mature protein by excision of the two terminal extensions by specific C and N terminal propeptidases Mature triple helical peptides then pack in a quarter D stagger to form the characteristic cross striated interstitial collagen fibrils.

The general structure of the helical protein is a repeating polymer of 330 glycine (Gly) XY sequences. Glycine regularly occurs in every third position to form a highly conserved central spine from which the X and Y residues project (X is often proline (10%) and Y often lysine (4%)). The interstitial genes are highly conserved and the exons are usually coded by multiples of nine base pairs (coding for the ancestral Gly XY tripeptide unit), most often of 54 base pairs, although varying from 45 to 152 base pairs[21–25] Presumably the Gly XY repeat is crucial, for the specific physical properties of the rigid collagen triple helix and possibly glycine mutations are either lethal or severely disabling. Particular post-translational modifications include lysine and proline hydroxylation, glycosylation of asparagine residues, and various crosslinkages between hydroxylated lysines. Genetic mutations of collagen α helices resemble those causing the haemoglobinopathies. They include amino acid substitutions,[27] gene insertions[28] and deletions[29 30] and various regulatory mutations with diminished or absent normal or mutant protein production[31–33] Deficiencies of enzymes catalysing collagen crosslinking or excision of either of the terminal propeptides have also been documented. So far the only convincing molecular defects have affected the genes and proteins for the α1(I), α2(I), and α1(III) products, although a type VII gene defect is strongly suspected in dystrophic epidermolysis bullosa and a family of large polymorphic deletions identified for the 3' end of the α1(II) gene. There may be technical problems in identifying specific protein mutations for cartilage collagen and basement membrane proteins (and genes) because of the difficulty of epithelial and cartilage cell culture from conventional biopsy specimens. Perhaps basement membrane and other mutations would act as genetic lethals in heterozygotes and homozygotes and would not be identifiable for this reason.

Type I collagen mutations

These characteristically produce inherited bone fragility (osteogenesis imperfecta) but have also been recently associated with Marfan's syndrome and Ehlers-Danlos syndrome type VII. These diseases share specific clinical features, such as hyperextensible skin and joints, blue sclera, pectus excavatum, scoliosis, and high palatal arches. Important distinguishing features include brittle, easily fractured bones, deafness and short stature (osteogenesis imperfecta), arachnodactyly, lens dislocations, and aortic rupture (Marfan's syndrome), and short stature and extreme joint extensibility associated with easily bruised fragile skin (Ehlers-Danlos syndrome type VII). Osteogenesis imperfecta (OI) is surprisingly diverse genetically, clinically, and especially biochemically. Sillence classified it into four main clinical groups, two of which are mild, autosomal dominant and of late onset, the others being severe, often lethal, and otherwise crippling[34] They are of early onset and are sometimes autosomal recessive (types II and III OI). Patients with type I OI have blue sclera in contrast to their type IV counterparts, who are white eyed. Both types are fairly mild diseases that are generally manifest after birth (OI tarda) and improving at puberty. Both types have specific variants, which breed true for the presence or absence of dentinogenesis imperfecta: unusually brittle discoloured teeth with disorganised, sparse dental tubules. Bone collagen is almost entirely type I, with traces of types III and V collagens, and all the convincing molecular defects so far identified have affected α1(I) or α2(I) collagen proteins and genes or have been in tight linkage disequilibrium with one of them.[35 36] There is no consistent correlation between the clinical type of OI and its molecular diseases. Thus cysteine point mutations can cause both lethal type II OI and mild OI tarda.[37 38]

Similarly, diminished type I collagen synthesis with increased III:I protein ratios can affect patients with lethal OI and mild OI tarda.[39 40] Other defects include a 500 base pair deletion in OI type IIa[29] and an arginine substitution in the C terminal propeptide associated with severely crippling type III OI (by interfering with mannosylation and secretion of the C propeptide),[41] a four base nonsense deletion in the C propeptide,[29 42 43] causing severely crippling OI type III (and premature osteoporosis in his heterozygous but clinically normal parents). A structural $\alpha 2(I)$ mutation in type II OI[44] and an N terminal $\alpha 2(I)$ deletion in type IV OI have also been documented [45]

Except for what Prockop calls suicide mutations, in which one of the three triple helical components disrupts its two normal companions (disturbing the proper winding, assembly, and melting profile of the fibre), there are no satisfactory biophysical explanations of how rather similar mutations can cause both OI tarda and OI lethal variants. An excellent example is the glycine to cysteine substitution, which causes lethal OI with an altered collagen type I melting profile (Tm), compared with a cysteine substitution, causing mild OI and no melting (helical disorganisation) of the collagen triple helix.[37 38] Possibly arginine or serine have mutated to cysteine in this instance, producing milder effects on the mature collagen molecule. A third mutation has been described, however, in which a cysteine substitution causes an altered melting profile but a mild form of disease (de Wet WJ. Personal communication, 1985) This raises the possibility that sometimes a second (so far undetected) mutation either in the collagen $\alpha 1(I)$ or some other major—for example, $\alpha 1(II)$—or minor cartilage collagen component, such as type X or type IV, could be causing a more severe compound disease. Alternatively, the cysteine substitutions are not the direct cause of the disease in this instance. Similar explanations may apply to those forms of lethal OI and mild tarda OI in which reduced III/I collagen protein and messenger ribonucleic acid concentrations cause lethal and mild disease with very similar mutations.

Type III collagen mutations

Defects of these genes and proteins are characterised by arterial rupture but have a disease range from a lethal premature aging syndrome (Ehlers-Danlos syndrome type IV—acrogenic pattern) to symptomless relatively normal looking patients with a mild deficiency accompanied by the benign hypermobile syndrome (Ehlers-Danlos syndrome type III) with superadded sacral striae, aortic rupture, and mitral valve prolapse. We have seen very similar biochemical deficiency in one British and two Belgian patients with Ehlers-Danlos syndrome type I. Patients with Ehlers-Danlos syndrome type IV have a strong predisposition to the lethal and unpredictable rupture of large or medium sized arteries. They share the common clinical feature of thin skin, premature aging, a typical facies with thin lips and unusually prominent eyes, abnormally easy bruising, cutaneous venous visibility, and capillary telangiectasia. Type III collagen protein is diminished to 5–50% of expected concentrations as measured by scanning polyacrylamide gel electrophoresis of glycine and proline ^3H or ^{14}C labelled skin fibroblast collagens Yet other variants produce mutant type III proteins[23] and perhaps a wide range of mutant proteins with amino acid substitutions, gene deletions, and inserts similar to those observed in OI await improved methods of protein fingerprinting and gene analysis. Certainly, phenocopies of type III deficiency with many of the clinical features of Ehlers-Danlos syndrome type IV but normal type III concentrations are common. We have also observed convincing clinical disease associated with normally migrating type III proteins tightly linked to polymorphic markers for the relevant gene (see below).

Other collagen protein deficiencies

So far no other disease linked mutations have been detected for a variety of other collagens, including types II, IV, V, VII, VIII, IX, and X proteins. We would expect type II collagen changes to be associated with short limbed dwarfisms, such as achondroplasia, pseudoachondroplasia, or spondyloepiphyseal dysplasia. The evidence linking the type II gene with achondroplasia is controversial, some authors having found positive linkage, while others have observed negative linkage in this disease [46 47] Type IV and VII collagen defects are good candidates for abnormalities in some lethal forms of epidermolysis bullosa, type X collagen may be associated with some forms of lethal osteogenesis imperfecta, and types VI and VIII collagen deficiency are causal candidates for certain arterial diseases, such as aortic and circle of Willis aneurysms as well as the Marfan's syndrome.

Restriction fragment length polymorphisms (RFLP)

Random variability in DNA sequences close by or within structural genes have been recognised as possible markers for human genetic disease. These are neutral changes that are usually causally unrelated to the disease but sufficiently close to the mutant gene to avoid meiotic crossing over An excellent example is the haptoglobin I restriction fragment variable site, which is tightly linked to the sickle cell gene and which will detect this gene reliably in 70% of affected black Americans.[48] This approach can be used whether or not the mutant gene is identified. Two recent exciting examples have linked important disabling genetic diseases such as Huntington's chorea[4] and cystic fibrosis[5 7] to RFLP, which segregate close enough to the candidate gene to be closely linked with it. The way is now clear for accurate prenatal diagnosis and prevention as well as the possibility of identification and analysis of the unknown gene in the foreseeable future. This approach has been useful in the following inherited abnormalities of collagen.

(1) α2(I) Gene polymorphisms: Eco RI,[49] MspI,[50] useful in type IV OI and implying the involvement of this gene in that disease; linkage with type I OI has also been recently described Bgl II and Eco RI markers are also available for this gene.[51]

(2) α1(III) Polymorphisms: an Eco RI polymorphism has been described in two American families with lethal autosomal dominant type III collagen deficient Ehlers-Danlos syndrome type IV.[52] A Msp/Ava I polymorphism maps to the same region of the gene[53] and has been successfully used to show linkage in a large Belgian kindred with a disease variant of Ehlers-Danlos syndrome type IV. (DePaepe A, Nicholls AC, Narcisi P, *et al.* Linkage of a polymorphic marker for the type III collagen gene (Col3A1) to autosomal dominant Ehlers-Danlos syndrome type IV in a large Belgian pedigree 1986.)

(3) α1(II) Polymorphisms: so far several polymorphisms have been identified in this large 38 Kb gene including Hind III and PvuII, polymorphisms of the 9.2 Kb Eco 1 fragment, which has not segregated with either dominant OI[54] or Ehlers-Danlos syndrome type II.[55] Secondly, a common Eco/RI/Bam HI polymorphism localised very close to the 3′ end of the gene shows substantial variability, probably due to deletions of segments of a hypervariable site The deletions range from 30–300 base pairs with occasional insertions in this site.[56] Deletions of these fragments have segregated both with lethal OI in some white families[57] as well as occurring in 10% of the British Asian populations,[58] presumably for reasons of genetic drift (selective advantage). We have also studied a Bam HI intragenic point polymorphism, which we have observed in over 20% of white patients with osteoarthritis compared with 10% and 0%, respectively, of two separate control samples.[59]

(4) Polymorphisms associated with the pro α1(I) gene have been remarkably elusive. Sykes and his colleagues have just published two polymorphisms associated with the 5′ end of the gene.[60] One, an Msp variable site, lies 30 Kb 5′ to the gene and has a population frequency of 0·23, while the other is less common and is an Rsa polymorphism within the 5′ end of the gene.

By using these pro α1(I) together with the pro α2(I) markers mentioned above, Sykes *et al* have confirmed the association of Sillence type I OI with both pro α1(I) and pro α2(I) collagen genes. The former had of course been implicated with this disease on the basis of protein data,[27 40 41 45] while the latter has been suspected both on protein[44 45] and linkage data[49] for several years

Other markers

The various cloned collagen genes are dispersed in several autosomal chromosomes, which include chromosome 17–α1(I) 7, α2(I), 2α1(III), α1(V), 12 α2(I), and 13 α1(IV). Markers close to the collagen genes on those chromosomes can also be used to study disease segregation and we can confidently expect that the genes for α1(VI), α1(VII), α1(VIII), α1(IX), and α1(X) will be similarly traced in the foreseeable future.

Prenatal diagnosis and prevention of all the specific molecular defects described above is already a practical possibility and the next few years should witness substantial advances in the management and prevention of common and uncommon diseases caused either directly by collagen gene mutations or lying close to them. These will include osteogenesis imperfecta, various Ehlers-Danlos mutants, some forms of Marfan's syndrome, certain short limbed dwarfisms, berry aneurysms of the circle of Willis, osteoarthritis, osteoporosis, keloid scarring, elastin gene defects, cystic fibrosis, and many others.

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Controversy

Ventilator settings for newborn infants

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The selection of appropriate mechanical ventilator settings for newborn infants is a controversial topic. The purpose of this review is to summarise the origins of the controversy and then to concentrate on the interaction between ventilator variables and the pathophysiology of the lung. As lung mechanics differ widely in different diseases we argue that careful consideration must be given to the mechanical properties of the lung when deciding on a suitable ventilator regimen for a particular infant.

Origin of early recommendations

Many years ago, one of us made recommendations for the ventilation of infants with severe hyaline membrane disease. These recommendations are still followed by some, but others claim that they promote pneumothoraces and that better results are obtained if different settings are used—notably, faster respiratory rates. If the current debate about how best to set ventilators is to be clarified the origin of the early recommendations must be understood.

Mechanical ventilation for newborn infants with respiratory failure became widespread in the late 1960s and early 1970s. Although it was immediately clear that the lives of preterm infants with recurrent attacks of apnoea and relatively normal lungs could be saved, great difficulty was encountered in infants with severe hyaline membrane disease (HMD)

The conventional way of setting the ventilator at that time was to select a rate of 60–80 breaths per minute for infants with HMD and if possible to synchronise the machine with the infant's own breathing pattern. At these rates the arterial carbon dioxide tension could usually be easily controlled but the oxygen tension could not, unless very high peak airway pressures (often 35–50 cm H_2O) were used.[1] The vast majority of the infants died, either rapidly of hypoxaemia or more slowly (at about 2 weeks of age) from an aggressive form of lung fibrosis, which was termed bronchopulmonary dysplasia.[2 3] Evidence was obtained from observations of ventilator variables and autopsy findings that the main cause of bronchopulmonary dysplasia at that time was distension and disruption of the terminal airways caused by the use of very high peak airway pressures.[3 4]

Experiments were therefore performed to see if ways could be found to ventilate babies with severe HMD at lower peak airway pressures.[5 6] Modified Bennett PR2 ventilators (time cycled, pressure limited, intermittent flow machines) were used, set to provide a plateau of peak airway pressure during inspiration. The major findings of these studies were that if a rather slow rate was selected (30 breaths/minute) arterial oxygen tension was higher than at a fast rate (an observation also made by Smith *et al*[7]) and that the oxygen tension could generally be raised further by manoeuvres that increased mean airway pressure, notably by increasing inspiration: expiration (I:E) ratio. Arterial carbon dioxide tension could most readily be manipulated by small changes in ventilator rate or in the difference between peak and end expiratory pressures (which altered alveolar ventilation).

These results were easy to relate to the pathophysiology of HMD. As the surfactant deficient lung is both poorly compliant and unstable, it is difficult to inflate and collapses readily during expiration. Atelectasis causing right to left shunting of blood through both intrapulmonary and extrapulmonary channels is responsible for most of the deficit of oxygen uptake.[8] Hence improvement of arterial oxygen tension was to be expected when peak airway pressure, I·E ratio, or positive end expiratory pressure were increased—the first strategy opening up collapsed lung units, the second holding them open for a greater part of each breath, and the third retarding alveolar collapse during expiration. The effect of slowing the ventilator rate in improving oxygen tension, though more complex, may in part have reflected the need for time as well as pressure for collapsed lung units to reinflate, because viscous and inertial forces must be overcome.[4 9] Any strategy that increases the duration of the inspiratory phase, such as decreasing rate or increasing I:E ratio (while maintaining other variables constant) should, within limits, promote alveolar inflation, reduce right to left shunt, and improve oxygenation.

These observations on the effects of different ventilator settings led to recommendations for the management of infants with severe HMD that were designed to avoid the use of very high peak airway pressures (>25 cm H_2O). This regimen was characterised by slow ventilator rates (30–40/min) and the use, when required, of prolonged inspiratory times (I E ratio ≥1 1) as a means for maintaining a satisfactory arterial oxygen tension[10–12] To keep peak airway pressure and I:E ratio as low as possible, very high inspired oxygen concentrations were often used. As soon as recovery started the ventilator pressures and inspired oxygen concentrations were both reduced. The introduction of this regimen at University College Hospital (UCH) was associated with an immediate large increase in survival that seemed to be attributable to a reduction in deaths from 'aggressive' bronchopulmonary dysplasia.[13]

Many reservations must be entertained when applying this regimen today. The experiments on which it was based were performed with an intermittent flow ventilator on infants who were selected for study because they had severe HMD; hence the regimen was recommended only for similar infants Also the observations on survival predated the regular use of continuous positive airway pressure and positive end expiratory pressure Perhaps the greatest change though has been in the population itself; the thresholds for mechanical ventilation have become much less stringent and extremely preterm infants form a far greater proportion of the population receiving ventilation. Nevertheless, it is interesting that at UCH, where we have used this regimen routinely for severe HMD since 1970, the change in population does not seem to have been associated with any appreciable change in the incidence of pneumothorax—the complication currently under most debate. Between 1979 and 1983 the incidence was 21% in 88 inborn infants with gestation of 24 to 32 weeks who were ventilated for HMD. (Ramsden CA, Stewart AL. Unpublished data.)

The controversy

Some authors have experienced high incidences of pneumothorax—up to 50%—in infants ventilated with slow rates and long inspiratory times,[14 15] and several publications have implied that the use of faster rates and shorter inspiratory times is associated with better results, including fewer cases of pneumothorax.[1–2]

Three studies have been particularly influential in popularising this view, but each suffers from problems of experimental design.[16–18] Bland *et al* reported only two cases of pneumothorax in 24 infants ventilated for HMD at 60–110/min but had no control group.[16] Spahr *et al* found a trend towards fewer air leaks in infants with HMD ventilated with I E ratios of 1:2 than in infants ventilated with ratios of 2:1, but no account was taken of the severity of the disease—infants were ventilated for an average of 80 hours with an I:E ratio of 2 1, even though an inspired oxygen concentration of less than 50% was required for 60% of that time[17] Heicher and her colleagues reported that in a consecutive series of 102 infants requiring ventilation for a variety of respiratory disorders pneumothoraces developed in only 14% of those ventilated at 60/min, significantly less than the 35% incidence in infants ventilated at 20–40/min[18] The maximum peak airway pressure allowed in infants ventilated at the fast rate, however, was 30 cm H_2O compared with 40 cm H_2O for the slower rate. More recently, Pohlandt *et al* have reported the preliminary results of a large multicentre trial comparing slow rates and long inspiratory times with fast rates and short inspiratory times[19] A lower incidence of pneumothorax was found when fast rates were used, but no account was taken of the diagnoses.

These studies illustrate very well two fundamental problems of trial design that lie at the heart of the present debate about ventilator settings. The first is lack of appreciation that the regimen summarised earlier was developed specifically for infants with severe HMD The use of slow rates and long inspiratory times in most other respiratory disorders or in mild or recovering HMD where the lung is fairly compliant and stable is certain to cause severe hyperinflation with disastrous results—notably, lung rupture and obstruction of the circulation.[12] The second and closely related problem is the enrolment of study groups unselected either by respiratory diagnosis or by the severity of the illness.

We believe that before further trials are undertaken it is vital that consideration is given in their design to the relation between ventilator variables and lung pathophysiology, the most crucial aspect of which is the relation between the expiratory time of the ventilator and the expiratory time constant of the respiratory system.

Time constant of the respiratory system

During conventional mechanical ventilation lung deflation usually occurs passively As the expiratory valve of the ventilator opens gas flows from the infant's lungs into the ventilator circuit propelled by the pressure gradient between the alveolar lumen and airway, which is generated by the elastic recoil of the lungs and chest wall.

The time taken for lung deflation depends on the magnitude of the elastic recoil (the inverse of compliance) and on the resistance of the airways. Decreased compliance shortens the time taken and increased airway resistance lengthens it

The time required for expiration is therefore directly related to compliance and resistance and can be expressed by the following equation:

$$\frac{Vt}{Vo}=e^{-\frac{t}{RC}}$$

where Vt is the volume remaining in the lung at time t after the onset of expiration, Vo is the total volume exhaled when expiration is complete, and e is a constant with the value 2·7183 R is airway resistance and C is compliance of the lungs and chest wall (see Appendix for derivation of this relation).

The product of compliance and resistance is often referred to as the time constant of the respiratory system (τ_{RS}) and is measured in units of time (seconds) τ_{RS} provides an index of the time necessary for deflation to occur, and its relevance to ventilation becomes apparent if we solve the above equation for various durations of expiration For example, when the duration of expiration 't' equals τ_{RS} then:

$$\frac{Vt}{Vo}=e^{-\frac{t}{\tau_{RS}}} \text{ or } \frac{Vt}{Vo}=2\cdot7183^{-1}=0\cdot37.$$

Thus after the passage of a single time constant 37% of the tidal volume remains to be expired. Similarly, we can calculate that after two, three, four, or five time constants have passed the proportion remaining is 13·5, 5·0, 1·8, and 0·7%, respectively

The value of τ_{RS} sets a limit to the minimum expiratory time that can be used without causing gas trapping. For practical purposes, a time equivalent to at least three time constants must be allowed if expiration is to be reasonably (95%) complete.

Time constant and disease state

As τ_{RS} is determined by the compliance and resistance of the respiratory system it varies widely according to the nature and severity of the respiratory illness

If we use published values of R and C[23–26] we can estimate the expected value of τ_{RS} for various respiratory disorders. It may be as short as 0·05 seconds in HMD (compliance ~ 1 ml/cm H_2O, resistance ~ 50 cm H_2O/l/sec), as long as 0·25 seconds in infants with normal lungs (compliance ~ 5 ml/cm H_2O, resistance ~ 50 cm H_2O/l/sec), and considerably longer in those with airways obstruction. For example, Grunstein *et al* recently estimated mean τ_{RS} to be 0·5 seconds in infants with chronic lung disease.[26] The time that must be allowed for expiration to occur during mechanical ventilation is therefore crucially dependent on the disease from which the infant suffers, varying more than fivefold between different diseases.

Positive end expiratory pressure (PEEP) and 'inadvertent PEEP'

If a ventilator expiratory time of less than $3\times\tau_{RS}$ is used—for example, <0·75 sec for normal lungs—substantial gas trapping will inevitably occur during expiration The effect of this is quite similar to the effect of applying PEEP and is often referred to as 'inadvertent PEEP'. Either measure will hold lung volume above the relaxed functional residual capacity—the functional residual capacity at zero inflation pressure—and may improve oxygenation if the relaxed capacity is abnormally low.

Despite this potentially beneficial effect (which newborn infants apparently set out to achieve for themselves during spontaneous breathing. See below.), we believe that inadvertent PEEP represents the major danger of employing fast rates during mechanical ventilation. Inadvertent PEEP is additive to the applied PEEP and carries no theoretical advantage over increasing the level of applied PEEP. Unlike applied PEEP, its magnitude can only be measured by sophisticated techniques, and it may be quite considerable: Simbruner and his colleagues have recently shown levels of inadvertent PEEP as high as 4–7 cm H_2O in infants ventilated for a variety of respiratory disorders at 30–40/min and with expiratory times of not less than 0·8 seconds.[27] Furthermore, because the value of τ_{RS} is not static throughout the course of a respiratory illness, the level of inadvertent PEEP will vary considerably, while ventilator settings remain unchanged. During the recovery phase of HMD, for example, the use of a fast rate at a time when the τ_{RS} is increasing rapidly may cause a dramatic rise in inadvertent PEEP with the risk of carbon dioxide retention, pneumothorax, and compression of the pulmonary circulation.[12]

Expiratory time

Although it is tempting to use published values of τ_{RS} to estimate the minimum expiratory time that can be used in various respiratory disorders without causing air trapping, considerable caution has to be exercised as several factors may alter the effective value of τ_{RS}. For example, τ_{RS} is increased by the additional resistance of the endotracheal tube, which is both variable (dependent on tube diameter and design) and unpredictable (due to the accumulation of secretions).[23 27] The presence of PEEP (inadvertent or applied), on the other hand, may shorten the time constant by decreasing resistance (splinting airways open) and decreasing compliance (by moving the tidal flow on to a higher and flatter part of the pressure-volume curve) The mechanical behaviour of the ventilator must also be considered. In particular, the exhalation valve takes a finite time to open, during which resistance is high and expiration is slowed: the opening time is only 0·04–0·07 seconds with the Sechrist or Bear Cub BP 2001 machines but can be as much as 0·28 seconds with the Baby Bird.[30]

Despite these reservations, it is sobering to make some rough calculations. The value of τ_{RS} in an intubated infant with normal lungs is about 0·25 seconds. Ventilated at 60 breaths/min with an I:E ratio of 1:1, almost 15% of the tidal volume will be trapped in expiration; at 100/min the proportion increases to 30%. The presence of secretions in the endotracheal tube can double respiratory system resistance;[28] in our last example this would increase the trapped proportion to 55%. Under such circumstances inadvertent PEEP would be very great. The crucial effect of lung disease on expiratory time is evident when similar calculations are performed for infants with respiratory illnesses, using values of τ_{RS} given earlier. An immediate visual meaning to τ_{RS} (as well as useful diagnostic information) is given by watching the rate of expiration in an ill infant: the lungs of an infant with severe HMD seem to collapse very rapidly, whereas those of an infant with meconium aspiration may seem to be almost fixed in inspiration.

Inspiratory time

Similar principles can be applied when considering the effect of manipulating ventilator inspiratory time. The factors affecting lung inflation are, however, more complex than for deflation and such an approach is rather crude. Nevertheless, two issues are quite important.

The first is that airway resistance is lower during inspiration than during expiration. Hence the inspiratory time necessary for lung inflation to be complete is considerably less than the corresponding expiratory time. During spontaneous breathing this effect is probably quite small, expiratory resistance being only 15–20% greater than the inspiratory resistance. Perez Fontan and his colleagues have recently reported, however, that during mechanical ventilation the combined mean expiratory resistance (respiratory system plus endotracheal tube) may be as much as 4·5 times greater than the mean inspiratory resistance.[30] This effect may be explained in part by airways being splinted open by the applied inspiratory pressure Such a striking difference between inspiratory and expiratory resistance favours gas trapping when the ventilator rate is increased; lung inflation will be complete with inspiratory times that are considerably less than the minimum effective expiratory time.

The second issue is that where atelectasis is present, as in HMD, inspiratory times considerably longer than those predicted from τ_{RS} may be required to overcome the forces that resist re-expansion of collapsed lung units (as discussed above)

Inhomogeneity of the lung

So far we have assumed that the lung behaves as if it was completely homogeneous—each lung unit operating in parallel, with an identical τ_{RS}. For many practical purposes this assumption seems warranted as a linear relation between volume and flow, implying a single value for τ_{RS} (see Appendix), has been found in normal infants and infants with HMD.[24 25] As ventilatory rate increases, however, progressive inhomogeneity of τ_{RS} becomes apparent, even in normal lungs, as shown by Helliesen *et al*[31] and Olinsky *et al*.[32] There are two important consequences. Firstly, as inspiratory time shortens lung units with relatively long values for τ_{RS} become less ventilated, leading to ventilation-perfusion imbalance, and secondly, as expiratory time shortens gas trapping develops in units with long values for τ_{RS}.

Gross inhomogeneity of the lung is present in certain disease states—notably, meconium aspiration, which causes widespread uneven airways obstruction—and in chronic lung disease, where both resistance and compliance vary widely throughout the lung, some areas being fibrotic and others emphysematous. Clearly, no single value of τ_{RS} can be assumed when considering how best to ventilate these infants.

For infants with severe meconium aspiration, it has been suggested that advantage can be taken of the inhomogeneity of τ_{RS}.[12] If a very short inspiratory time is used lung units with fairly short values for τ_{RS}—that is, the relatively less obstructed areas of lung—will be preferentially ventilated, thus avoiding, partly at least, the dangerous complication of severe gas trapping distal to the obstructions.

Spontaneous breathing

Infants often continue to make active respiratory efforts during mechanical ventilation, and several studies suggest that this activity increases the risk of pneumothorax[35] and cerebral haemorrhage.[34] A particular pattern of interaction between infant and ventilator, so called 'active expiration', has recently been implicated as responsible,[33] though the mechanism by which this interaction causes pneumothorax remains uncertain.[35] In a population of infants with this behaviour Greenough *et al* found that muscle relaxation with pancuronium almost completely prevented pneumothorax (one case in 11 infants), whereas all 11 comparable controls developed this complication.[33]

It is often suggested that faster ventilator rates promote 'synchrony' between infant and ventilator While this may be a common clinical impression, surprisingly little experimental evidence is available to confirm it. Both Greenough *et al* and Field *et al* have shown some increase in the time spent in apnoea or synchronous breathing when fast ventilator rates were employed, but neither group attempted to keep the major variable affecting respiratory drive constant—namely, the carbon dioxide tension.[20–22] Intuitively, it may seem reasonable to attempt to match ventilator timing to the infant's own spontaneous ventilatory cycle. Given that the control of breathing, however, depends on complex interactions between reflex responses—for example, Hering-Breuer reflex, carbon dioxide tension, sleep state, and behavioural factors—there may be a temptation to expect no more than transitory success.

There is increasing evidence that the spontaneously breathing infant (like the mouse[37]) uses a rapid respiratory rate as a means of preventing airway closure in expiration.[36] By employing a rapid rate and a very short expiratory time (considerably less than $3\times\tau_{RS}$), complete expiration is prevented, a larger functional residual capacity is maintained, and oxygenation is improved. Attempts to achieve the same effect with a mechanical ventilator, as discussed above under 'inadvertent PEEP', are fraught with danger. Both the applied force (inadvertent PEEP) and its desired effect (raised functional residual capacity) are difficult to measure. The situation is quite unlike that of the spontaneously breathing infant whose lungs are liberally endowed with stretch receptors providing the feedback information necessary to modulate respiratory timing in accordance with the changing lung mechanics.

Conclusions

The arguments and calculations presented here are no more than illustrative, but we suggest that they show the difficulties of selecting appropriate ventilator settings for newborn infants and the folly of performing clinical trials that compare ventilator regimens in mixed populations of infants. The results of these trials must depend as much on the characteristics of the population as on the treatment applied· important beneficial effects in infants with one type of illness may be completely submerged by adverse effects in another We contend that only far more carefully designed and disease specific trials will provide any useful answers to questions about what type of ventilation to use or how best to set the ventilator variables. Wherever possible, measurements of lung mechanics, including τ_{RS}, as well as blood gases, should be employed in these trials so that the true effects of ventilation can be assessed.

Our own practice, pending further information, is based on the principles outlined above. We decide on what pattern of ventilation to use according to the respiratory problem from which the infant suffers; in so doing we hope to obtain satisfactory blood gases by tailoring the ventilator settings to suit the infant's lung mechanics. In general, we use the same disease specific guidelines as described in detail in 1979.[12] We rarely use rates greater than 40/min. We watch the infant's chest movements carefully to be sure that the lung is inflating and to assess whether expiration seems complete before the next ventilator breath: a visual clue about the duration of τ_{RS} can thus be obtained and the risks of inadvertent PEEP and gas trapping minimised. We often use pancuronium for muscle relaxation in the larger infants but are wary of it in the smallest ones.[38]

One important issue not touched on here is the potential place of ventilation of newborn infants by high frequency oscillation:[39] it is at present too early to draw firm conclusions about this very promising technique.

Appendix

According to the equation of motion of the respiratory system

$$P=\frac{V}{C}+R\dot{V} \qquad (1)$$

where P is the distending pressure (airway pressure during intermittent positive pressure ventilation), C the compliance, and R the resistance of the lungs and chest wall. V represents the volume above functional residual capacity and $\dot{V}$ the rate of gas flow measured at the airway opening.

At the onset of a passive expiration P falls to zero and equation (1) can be rearranged to give

$$\frac{V}{\dot{V}}=-RC$$

or

$$V=-V\tau_{RS} \qquad (2)$$

This relation is exploited in single breath studies of lung mechanics. If flow is plotted against expired volume a straight line is obtained, from which τ_{RS} can be derived. Note, however, that a linear relation between V and $\dot{V}$ will only be evident where the lung is homogeneous with a single value for τ_{RS}.[24 25]

Integration of equation (2) yields

$$\frac{Vt}{Vo}=e^{-\frac{t}{RC}}$$

from which the volume of gas still present in the lungs, Vt, at any time t, after the onset of expiration can be calculated (Vo is the total volume expired at the end of a complete expiration).

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Commentaries

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Ramsden and Reynolds highlight the dilemma faced by all those who ventilate ill babies. They suggest from some of the publications, theoretical calculations, and their experience that long inspiratory times and slow rates (30–40/minute) are the best way to ventilate babies with severe respiratory distress syndrome (RDS). Unfortunately, they discount fast rate ventilation (60–100/minute) without producing satisfactory evidence to show it is harmful

The studies of Reynolds in the early '70s, when ventilation was relatively new, involved babies who were apnoeic, were unresponsive to hand ventilation, and required high oxygen concentrations. Small numbers were studied; six in one paper[1] and nine in another.[2] They were not randomised and no account was taken of changes with time. Since then, ventilators have improved, the babies cared for are smaller, and the indications for ventilation less extreme

The authors cite and dismiss nine papers that reported improvements with fast ventilator rates. Some of these had large numbers (Spahr 69, Pohlandt 96, and Heicher 102), and were randomised. They are criticised by Ramsden and Reynolds because 'no account was taken of the diagnoses'. Despite varied causes for respiratory failure, these trials showed that fast rate ventilation resulted in less pneumothoraces, better oxygenation, and lower peak pressures.

The main thrust of Ramsden and Reynolds' argument against fast rates is that they may result in gas trapping, carbon dioxide retention, pneumothoraces, and compromised circulation. They calculate time constants for neonatal lungs based on passive lung mechanics. Unfortunately, this ignores the fact that most ventilated babies breathe spontaneously,[3] often expiring actively.[4] This effectively shortens the time constants and reduces the likelihood of excessive gas trapping. They present 'rough calculations', which indeed are 'sobering' if babies with healthy lungs were ventilated at 100 breaths per minute. If the compliance and resistance given for babies with RDS are used in these calculations, however, expiratory times could be as short as 0·15 seconds. Complete expiration would then occur at a rate of 100/minute without gas trapping.

The major abnormality in RDS is atelectasis and low lung volume. The more severe the lung disease, the faster the babies breathe and the shorter their expiratory time.[3] In this situation spontaneous fast respiratory rates predispose to gas trapping, thereby maintaining lung volume during expiration. There is no evidence that excess gas trapping occurs in spontaneously breathing babies with RDS.

Most babies breathe while being ventilated.[5] At ventilator rates of 30–40 cycles per minute this is usually asynchronous with the ventilator and may increase the risk of pneumothorax or intraventricular haemorrhage At faster rates babies spend more time breathing synchronously with the ventilator. Many do so continuously except when disturbed.[6]

Ramsden and Reynolds claim to base their ventilation technique on the time constants of their patients but describe no measurements of these. Measurements in ventilated premature babies are difficult and not practical for clinical use. They conclude that in general they follow the guidelines described in 1979 (slow rates with prolonged inspiratory expiratory ratios).[7] They state, however, that the use of slow rates and long inspiratory times in conditions other than severe RDS 'is certain to cause severe hyperinflation with disastrous results'. As babies with severe RDS are the minority presumably they would agree that this ventilation technique is unsuitable for most ventilated babies.

Unlike the authors, we are unable to make an early diagnosis of the cause of the respiratory failure. Neither can we detect complete expiration visually. Assessment of the publications and our studies of neonatal ventilation leads us to believe that most babies with RDS are best ventilated at fast rates. We now tailor the ventilation to the severity of the baby's illness by monitoring continuously the spontaneous respiratory timing, using this as a basis for the ventilator inspiratory and expiratory times. Thus as the lung disease improves spontaneous respiratory rate falls and the ventilator rate is reduced, eliminating excessive gas trapping. In our experience rapid rate ventilation often allows lower ventilatory pressures and does not cause overinflation or carbon dioxide retention and the incidence of pneumothorax is low. Babies breathing at the same rate as the ventilator are more settled.

Much more clinical research is required to elucidate the appropriate ventilator settings for use in neonatal respiratory failure.

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The review by Ramsden and Reynolds must be welcomed as it provides a thoughtful and, on the whole, balanced assessment of our current knowledge on how best to ventilate newborn infants. As our knowledge is incomplete, however, it is possible to examine the results of data available in a somewhat different light and to adopt a different, although I consider equally defensible, position.

The authors are rightly critical of the trials that have been carried out. This is inevitable as there are so many variables, so that it is extremely difficult to obtain data that are totally clear cut. They do not emphasise, however, that the two studies on which they base their present position are equally open to criticism. Their initial and now classic studies[1] purely explored the effects of different ventilator settings on blood gases and found that with the ventilators then available and the relatively mature babies in the neonatal units (all had birth weights over 1000 g) oxygenation improved at relatively low respiratory rates and long inspiratory.expiratory (IE) ratios. Recent studies, using similar experimental design but with better ventilators and more immature babies. have found that oxygenation and carbon dioxide excretion can be better at rates as high as 100 to 120/minute, although there is little evidence to suggest that rates above 60/minute are beneficial unless the baby is making respiratory efforts that are out of phase with the ventilator[2 3] The second study, from Professor Reynolds' unit, showing that slow ventilator rates led to improved mortality, used historical controls.[4] I know that the authors would be the first to admit that this is far from ideal

The authors place considerable emphasis on the need to allow sufficient time for expiration (and inspiration) to occur to avoid inevitable (alveolar) positive and expiratory pressure (PEEP) and allow maximal tidal exchange to occur for a given inflation pressure. Their claim that the time allowed for a volume change to occur must exceed three times the time constant is open to challenge. If, for example, only twice the time constant is allowed the calculated fall in tidal volume (13%) will be more than compensated for by the increased respiratory rate,
so that alveolar ventilation will rise rather
It is also extremely unlikely that a PEEP
the inflation pressure will be 'fraught witl
The authors correctly point out that high
lead to problems if used in babies with noı
and, even more, in those with airways ob
High rate ventilation is not being recon
however, for babies other than those wi
idiopathic respiratory distress syndrome
who have short time constants, the same
that the authors make on the use of long i
times. Although the studies published
from design faults,[5–7] it is interesting to no
found a reduction in the incidence of pneu
with high rates and not the reverse as pre
the time constant model of Ramsden and

In conclusion, we consider that the evide
able supports our current clinical practice
initial ventilator settings of 60/minute w
ratio of 1.1 and inflation pressures of 18–
babies with severe IRDS. If the baby fail
on these settings and continues to make r
effort against the ventilator we increase t
100–120 with IE ratios of 1:1·2.[8] If this r
does not lead to an improvement in oxyg
relatively rare event, we paralyse the
pancuronium and revert to rates of 60/mı
rates are reduced as soon as the clinical co
the baby permits.

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Response

C A RAMSDEN AND E O R REYNOLDS

Department of Paediatrics, University College, London

'There are more ways of killing a cat than choking her with cream'[1]

We are delighted that our article has prompted such lively discussion and glad to have the opportunity to respond to some of the comments made by Professor Milner and Drs Morley and South. We certainly do not discount fast rate ventilation, as stated by the latter authors; rather, we wish to present arguments about the relation between ventilator settings and lung mechanics that bear heavily on the selection of appropriate settings in different illnesses.

We welcome support from both commentaries for our own reservations about the present day use of techniques derived from studies performed many years ago,[2 3] and we certainly agree that these studies are open to criticism. We do not, however, understand Drs Morley and South's strictures about randomisation and changes with time. The questions that were addressed were to do with exploring the alterations in blood gases and other variables that took place after changes in ventilator settings in babies selected for study because of severe hyaline membrane disease (HMD). There would be no purpose in randomising the babies: the alterations in settings *were*, in fact, randomised, within the hypotheses being tested, and observations were made after a standard time. It is true, of course, that the use of historical controls in another study[4] was not ideal, as argued by Professor Milner. The reasons for adopting this approach were given at the time and also debated at length subsequently.[5] The data were, however, collected prospectively and the pathological studies performed 'blind'.

We think Professor Milner would concede that historical controls are better than no controls at all—a feature of some of the papers that Drs Morley and South believe we unfairly dismissed. In three of these papers,[6-8] Drs Morley and South draw special attention to the enrolment of large numbers of babies and to randomisation, but they seem to discount our concerns about the importance of diagnosis. We strongly challenge this stance, as argued in our article.

We also do not accept Professor Milner's assertion that the results of the recent trials are the reverse of those predicted from a consideration of time constants. These trials used inappropriately long inspiratory times in infants who did not necessarily have bad HMD—a measure that can be expected to have caused severe hyperinflation. We reiterate that lumping all conditions together may cause any beneficial effects in one illness to be completely submerged by adverse effects in another. The results of trials of this sort can tell us only that if we were to ignore the diagnosis and ventilate all infants in the same way then fast rates may cause less pneumothoraces than slow rates. Where the diagnosis is not known (a problem that Drs Morley and South consider to be perhaps more common than we do) this information could be of value, but it is not really what we want to know when deciding how best to ventilate an infant who clearly has, say, severe HMD, meconium aspiration, or apnoea with normal lungs.

We agree with Drs Morley and South that gas trapping is unlikely at fast rates in severe HMD and also with Professor Milner's view that inadvertent positive end expiratory pressure (PEEP) amounting to 13% of peak airway pressure is unlikely to be harmful, but we think there is little evidence to support his statement that fast rates are being recommended only for infants with severe HMD. And even these infants, ventilated according to Professor Milner's protocol at a rate of 120/minute, which would yield an expiratory time of 0·27 seconds, would be vulnerable to excessive inadvertent PEEP if recovery began or secretions accumulated in the endotracheal tube.[9] Only one τ_{RS} might then be available for expiration and 30% or more of the peak pressure would remain as inadvertent PEEP.

We agree with both commentaries that the interaction between spontaneous and ventilator breaths is an important issue. We are puzzled, though, by Drs Morley and South's suggestion that this effectively shortens time constants. Synchronous respiratory efforts may hasten the rate of change of lung volume, but efforts that are out of phase will have the opposite effect. Undoubtedly, if synchrony can be achieved by fast rates then this is an important benefit. We have discussed the paucity of data on this point, and we note that Drs Morley and South refer to their own recent paper[10] on this matter (published when our article was in press): this paper provides data only on a single infant, though a total of 20 are said to have shown similar results.

We of course heartily welcome Drs Morley and South's closing remarks. We do not think that the available information strongly favours any particular regimen. Our own regimen[11] does not, incidentally, involve only the use of slow rates and long inspirations, as inferred by Drs Morley and South. We come back to our view that techniques of ventilation and clinical trials should be sensitive to what is known about lung pathophysiology and lung mechanics and should not be undertaken as though the lung in normal infants and in infants with all sorts of different illnesses may be expected to behave in the same way.

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Archives of Disease in Childhood, 1987, **62,** 539–541

Correspondence

Anaemia and child health surveillance

Sir,

Professor Illingworth's 'state of the art' review of iron deficiency anaemia[1] raised important issues of prevention but poses more questions than it answers, some of which are addressed in a recent *Lancet* editorial.[2] Should haemoglobin estimation be a screening test in childhood, and if so what technique should be used? What dietary strategies might best prevent anaemia (and the accompanying psychomotor delay)? There is also a wider question: what investigations should be available for children at primary care level, and should they be in general practitioner surgeries or clinics, or both?

It would be good to see a consensus emerging from within the British Paediatric Association on these questions to guide primary care practice. Some basic community research will be needed, however, to establish: (1) the best age to test for anaemia; (2) the most suitable technique to use and whether it will be clinic or central laboratory based; (3) the nature of the diet that leads to anaemia in different populations; and (4) the acceptability and practicability of a blood test as part of routine surveillance. Quality control is the stumbling block in establishing peripheral diagnostic facilities such as haemoglobin estimation, urine microscopy, and stool analysis, but the esculating demands on hospital laboratory services must surely point us in this direction.

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Age specific xerophthalmia rates among displaced Ethiopians

Sir,

In his paper Dr Pizzarello reports the eye signs that he found in 1200 displaced Ethiopian children and that he attributed to vitamin A deficiency.[1] The results were analysed by sex and for age groups 0–6 years and 7–14 years. The rates of Bitot's spots and corneal xerosis in all groups, as well as those for keratomalacia and corneal scars, far exceeded those suggested by the World Health Organisation (WHO)[2] as criteria for recognition of a public health problem. His conclusion that vitamin A deficiency was a serious problem in those aged 7–14, as well as in those aged 0–6, must not be allowed to go unchallenged. Interestingly enough, the first clear demonstration of the lack of relation between Bitot's spots and active vitamin A deficiency in school age children was carried out nearly 30 years ago in Ethiopia.[2] This observation has since been repeatedly confirmed from other parts of the world.[3] [4] At least some of the Bitot's spots in older children seem to be stigmata of vitamin A deficiency in the past,[5] and this may account for the rise in incidence with increasing age, commonly reported, as here. This is why WHO insisted that the subject group for prevalence surveys should be preschool age children.[2]

Another disturbing feature of this paper concerns the other criterion for coming to this conclusion—namely, corneal xerosis (X2). During the many discussions that I have had over the years with other workers experienced in the ocular manifestations of vitamin A deficiency, it has always been agreed that X2 (as the most advanced eye change present) is quite rare, probably because it advances rapidly to keratomalacia (X3A or B). Furthermore, without a slit lamp it is usually difficult to know whether or not a cornea is xerotic. For these reasons X2 is included with X3A+B in the WHO criteria.[2] The high incidences for X2 reported here are most unusual. All of this is not to minimise the serious problem of the occurrence of vitamin A deficiency in refugee populations. Although the WHO guidelines have not been engraved on tablets of stone, they have been drawn up after prolonged and detailed consideration of the available evidence. They should be read carefully and followed strictly; if then they can be shown to be in need of revisions this will happen if new data necessitate it.

Figures 1 and 2 have been incorrectly labelled.

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Dr Pizzarello comments:

I agree with Dr McLaren that the rates of xerophthalmia in the age group 0–6 far exceeded WHO guidelines but consider that the data support the presence of the disease in older children as well. Clearly, Bitot's spots do not always indicate the presence of active xerophthalmia in children over 6, a point made in the original paper. The extent of severe malnutrition in all age groups prompted me to examine children up to 14 in this population. It was an unprecedented situation, which I thought merited a wider sample size than normally used.

While Dr McLaren thinks that corneal xerosis cannot be diagnosed without a slit lamp, numerous other investigators have reported corneal xerosis in prevalence surveys performed without a slit lamp. In fact, the WHO 'Field guide to the detection and control of xerophthalmia' states that '(corneal xerosis) is easily diagnosed and highly specific' and makes no mention of the use of a slit lamp to make this diagnosis.[1] I feel confident in the diagnosis as stated in the paper.

Finally, and most disturbing, is the point made by Dr McLaren that while the WHO guidelines are not engraved on stone tablets, they should stand until new data become available. The point of this paper is to suggest that in severe disaster situations just such a revision may be indicated. It is time for this issue to be discussed in an open forum to prepare for the next disaster, which most unwelcomely and assuredly will arise.

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Meningitis presenting as hypertension

Sir,

I have just read the report by Waters and Gillis of meningitis presenting as hypertension.[1] A month ago I was called urgently to see a child with haemophilus meningitis who had developed severe hypertension. The hypertension was cured instantly by using an appropriately sized sphygmomanometer cuff. Reports involving blood pressure measurement in children should always give precise details of how the blood pressure was measured.

Reference

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Meningitis due to *Haemophilus influenzae* type b resistant to ampicillin and chloramphenicol

Sir,

The recent report by Fraise *et al* of multiply resistant *Haemophilus influenzae*[1] makes reference to two previous reports of resistance found in this organism from the United Kingdom[2] and the United States.[3] I suspect the authors did not take the time to read the reference for the USA. If they had it would have been clear that it was describing resistance in Australia, a country not easily confused with the USA. Even correct reading of the title should have made the error apparent.

Chloramphenicol resistance is now widespread, including reports from Thailand,[4] the USA,[5] and the Caribbean.[6]

Readers are entitled not only to accuracy of data but also to diligence and care of presentation.

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Drs Fraise, Meeks, and Richards comment:

We have read with interest the comments made by Dr Forsyth. We acknowledge that there was an omission in the introductory phrase of our paper, which should have read '. . . in the United States and in Australia.' We do not believe a small omission such as this, however, changes in any way the validity of our report or the message it contains.

This correspondence is now closed—ed.

Thrombotest values and effect of vitamin K administration for infants

Sir,

The finding of Garrow *et al* that Thrombotest values decline on the second day of life in breast fed babies but not in those who have received vitamin K at birth is important.[1] Fetal haemorrhagic episodes, including intracranial haemorrhage, are more common at 2 to 3 weeks of age than in the early days of the neonatal period.[2] Thus the Thrombotest for babies at 2 weeks may also be useful to predict and manage vitamin K deficiency.

We performed the Thrombotest (Thrombotest Owren, Eisai Co, Tokyo) for 437 babies at 2 weeks. Of the 437 babies, 263 were breast fed, 37 bottle fed, and 137 mixed fed. None of the babies had received vitamin K at any time before this study. A significant difference in the Thrombotest values of breast fed compared with bottle and mixed fed babies was obtained (mean (SD) Thrombotest values for breast fed babies=64·1 (20·0)%, for bottle fed=80·0 (22·7)%, and for mixed fed=73·9 (21·2)%; $p<0·01$). Four of the 263 breast fed babies had Thrombotest values lower than 30% and these babies may be at risk from intracranial haemorrhage.

We prescribed 2 mg of vitamin K_2 intramuscularly or orally to 125 babies (90 breast fed, five bottle fed, and 30 mixed fed) who had low Thrombotest values of less than 60% at 2 weeks. The mean (SD) Thrombotest values for babies with each feed before and two weeks after the vitamin K_2 administration were 48·3 (10·0)% and 88·2 (17·4)% for breast fed babies, 52·4 (8·4)% and 86·5 (16·7)% for bottle fed babies, and 50·0 (6·4)% and 93·0 (11·2)% for mixed fed babies, respectively. Thus the administration of vitamin K increased Thrombotest values and may be effective for the treatment of vitamin K deficiency in babies who are breast, bottle, or mixed fed. The possibility of the spontaneous resolution of vitamin K deficiency cannot be absolutely excluded. Recently, O'Conner *et al* showed that oral administration of vitamin K is also effective for the baby with vitamin K deficiency.[3] In our studies, 110 of the 125 babies who received vitamin K orally showed a similar increase in the Thrombotest values to those of intramuscular administration.

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Neonatal malaria and obstructive jaundice

Sir,

We enjoyed reading Davenport's paper entitled "Neonatal malaria and obstructive jaundice" in this journal.[1] We question the use of the term "obstructive jaundice". In Davenport's case there was no extrahepatic obstruction with bile plug. We believe, therefore, that the term "cholestatic neonatal jaundice" should be used in such a condition as we have suggested previously.[2]

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Dr Davenport comments:

Although I can see the objection to the term 'obstructive jaundice'[1] on the basis that a normal cholangiographic biliary tree is perfectly acceptable, I would like to justify the term on two counts.

Firstly, it is a widely used and understood term and seems more elegant than the biochemically equivalent 'conjugated hyperbilirubinaemia'. It implies a certain pattern of liver function tests—that is, conjugated bilirubin concentration, high alkaline phosphatase activity, and near normal hepatic enzyme activities.

Secondly, microscopically, canalicular cholestasis and intracellular biliary stasis point to a functional obstruction to the excretion of bile after intrahepatocellular conjugation, albeit with a patent extrahepatic biliary tree.

Thus it seems that the term can be retained with some justification on pathological grounds.[2]

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Archives of Disease in Childhood, 1987, **62,** 542

British paediatrics

Child abuse

Two draft documents, 'Child abuse: working together for the protection of children' and 'Child abuse: working together—a guide to interagency cooperation', have recently been referred to the British Paediatric Association (BPA) by the Department of Health and Social Security (DHSS). The BPA welcomes these documents, which provide helpful guidelines for professional agencies, but considers that they underestimate the vital role of paediatricians, who usually hold the key position in the diagnosis of child abuse and neglect. The DHSS recommendations should therefore be amended to encourage staff in accident and emergency departments to seek paediatric advice rather than refer to other specialist colleagues who may be more familiar with the specific injuries than with the problem as a whole. In many cases continuing paediatric and child psychiatric support is also vital.

The suggested change in name of the 'Child Abuse Register' to the 'Child Protection Register' will, the BPA hopes, reflect a shift in emphasis towards identifying children at risk. Information on the register should be readily available at all times to all medical staff who treat children.

The role of the community child health services is acknowledged in the draft documents, and the BPA believes that the increasing number of consultant paediatricians who have responsibilities for community child health will enable the community service to provide the necessary support and surveillance at a specialist level. The consultant should also act as the link between health, social, and education services. Each school should have a named doctor who would be notified of children at risk in the school. The proposal for increased involvement of general practitioners in child abuse is welcomed by the BPA, but it is essential that they be adequately trained.

Case conferences should be attended only by those working with the child and the family, who can give first hand information and focus on the interests of the child. The social worker should be accompanied, however, by a senior who is able to make decisions about management. The time needed to attend case conferences must be taken into account in assessing the workload of consultant paediatricians and their staff, and secretarial help must be provided if the proceedings of the conference are to be properly recorded. Although parents must be fully informed of the results of case conferences, the BPA does not consider that parents should normally attend.

The BPA wishes to retain the area review committee system under the social services department rather than set up joint consultative committees, which would have no legal status or responsibility.

Detailed arrangements for dealing with child sexual abuse need to be worked out locally and a BPA joint standing committee with the British Association of Paediatric Surgeons is currently drawing up a suitable scheme. Examination of children suspected of being sexually abused should be carried out in hospitals or health centres rather than in police stations, and paediatricians who perform these examinations must be adequately trained to collect forensic evidence.

The BPA recommends an increase in the number of special centres with experience in particular types of child abuse. They might, for example, be established on a regional basis to advise on difficult cases and promote education and training.

These documents are accepted by the BPA as a guide to good practice but their recommendations could be ignored when expedient. They should not be used as substitutes for legislation to protect children. As always, developing an effective service has resource implications and these must be recognised.

A D M Jackson

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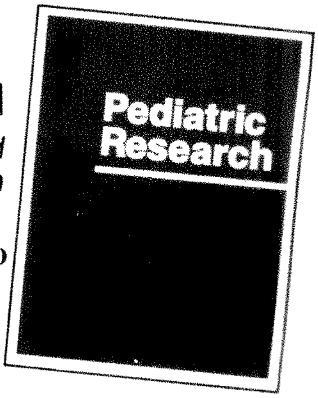

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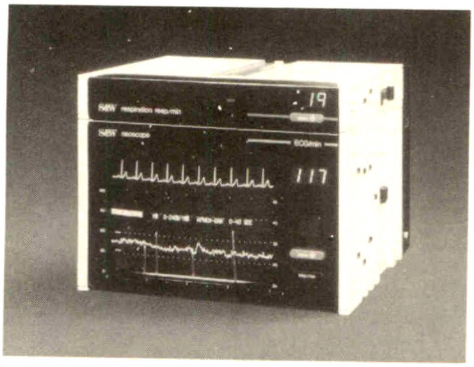

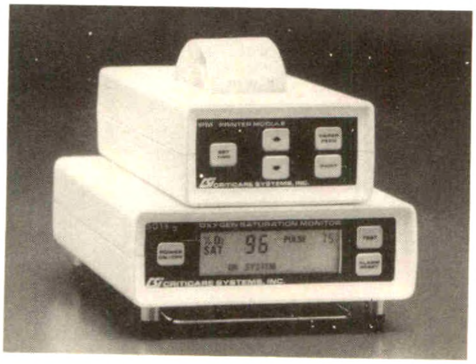

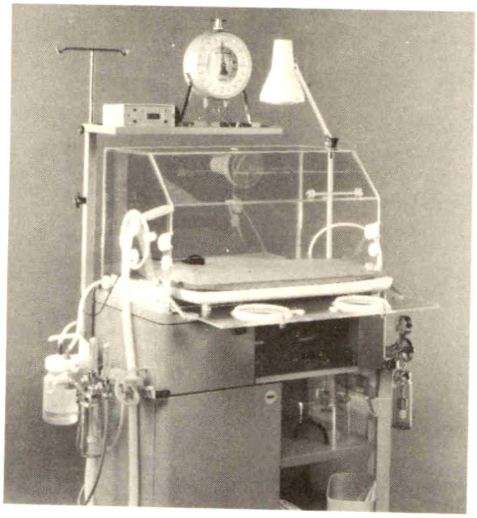

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Archives of Disease in Childhood, 1987, **62**, 543

A new editor

Dr M L Chiswick has been appointed joint editor of 'The Archives'. For the past 11 years he has been consultant paediatrician to the Northwestern Regional Perinatal Centre at St Mary's Hospital, Manchester.

Malcolm Chiswick has made important contributions to research, education, and the organisation of patient care. His MD thesis on the development of pulmonary surfactant showed how an animal model could provide an insight into neonatal physiology, as well as the importance of careful design before a study starts. His investigations into the causes and prevention of perinatal morbidity have emphasised that obstetricians and paediatricians need to share clinical experience. He is chairman of the standing joint committee of the British Paediatric Association and the Royal College of Obstetricians and Gynaecologists, secretary of the British Association of Perinatal Medicine, and secretary of the Royal College of Physicians Working Party on Neonatal Services. He has been the editor of two editions of *Recent Advances in Perinatal Medicine*, and published books on neonatal medicine. During the past two years he has been associate editor of The *Archives of Disease in Childhood*.

His extensive experience in research and clinical care of older children and newborn infants, together with his skill as a writer should ensure that 'The Archives' has an editor of the highest calibre.

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Annotations

Respiratory syncytial virus and the infant immune response

The pattern of disease caused by respiratory syncytial (RS) virus is distinctive. Severe lower respiratory tract infection, commonly bronchiolitis, is most prevalent among infants between 1 and 6 months of age. Primary infection outside of this age range is fairly common and well documented, but both neonates and children tend to handle the virus more successfully. One infection is insufficient to engender complete protection, but the severity of disease diminishes with successive infections as the child grows older.[1]

The search for an explanation of this unique epidemiological pattern has centred on the infant's immune response: effectively, all mothers will have encountered this ubiquitous virus and vulnerable infants passively acquire maternal immunity both transplacentally and, in some cases, through colostrum and breast milk. In addition, they are capable of mounting their own primary local and systemic responses. For babies who develop bronchiolitis the complex interaction of these passive and active defences results in an aggregate response insufficient to protect the lung from damage. Recent research has revealed several subtle defects, some age related and some RS virus specific, which together may begin to explain why patients with this virus fill our paediatric wards each winter.

Transplacental antibody

Babies acquire serum antibody passively from their mothers, and there is evidence that high maternal antibody concentrations may protect.[2] The incidence of severe infection rises, however, from the second month of life when concentrations of maternal antibody in infant serum are still high. No satisfactory explanation for this phenomenon is yet available, but there are several ways in which maternally acquired antibody may be inadequate.

It has been suggested that protection of the infant lung against RS virus is mediated by antibody of the IgG3 subclass. IgG3 forms a minor component of the antibody acquired transplacentally, has a short half life, and declines to a nadir in infant serum at four to six weeks of life.[3] Acute serum samples from infants infected with RS virus have been found to contain IgG3 anti-RS virus antibodies, albeit at low concentrations, but it might be argued that these have declined below a threshold necessary for protection.[4] Alternatively, transplacentally acquired antibody may lack specificity for the strain of virus infecting the infant. RS virus is not monotypic and at least two subtypes have been described that have co-circulated during recent years.[5] Studies in animals indicate that cross protection does occur but does not correlate with neutralising antibody concentrations and may depend on cross reactive cell mediated immunity, which does not cross the placenta.[6]

To protect the infant, antibody present in the blood must gain access to the site of infection. Enhanced transudation of serum immunoglobulin on to the mucosa occurs during the early inflammatory response to virus. Exposure of human macrophages to RS virus, but not influenza virus, stimulates production of an interleukin 1 inhibitor, which in vivo may delay inflammatory changes at the site of infection and thus hinder mobilisation of serum antibody.[7]

Bronchiolitis and breast feeding

Immunity to RS virus may also be acquired passively from the mother through breast milk, and breast feeding reduces the risk of lower respiratory tract disease.[8] Colostrum and milk contain large amounts of IgA antibody, some of which is RS virus specific, and breast fed but not bottle fed neonates have IgA in their nasal secretions, which is probably passively acquired. Lower concentrations of anti-RS virus IgG antibodies are also found in milk and RS virus reactive T lymphocytes are present in the colostrum of up to 40% of mothers. Mothers of infants with severe RS virus bronchiolitis were no more likely, however, to have low anti-viral IgA or IgG antibody concentrations or lymphocyte reactivity in their colostrum and milk than mothers of infants with mild disease or infants of similar age with no evidence of infection.[9] Animal studies have indicated that breast feeding may accelerate the maturation of the infant mucosal immune response, but in human infants we have found that nasal antibody responses in breast and formula fed infants with RS virus infection were similar both in timing and concentration. The mechanism of protection afforded by breast feeding thus remains obscure.

The infant's systemic immune response

Detailed recent comparisons of serum antibody responses of infants and older children have shown no significant qualitative differences in either immunoglobulin subclass or antigenic specificity.[10 11] After primary infection with RS virus, however, serum antibody responses of infants are less efficient than those of older children. Some fail to respond at all and the low level and inconsistency of their systemic response probably contributes to their vulnerability to the virus.[10] The poor serum antibody response of infants may, at least in part, result from an immunosuppressive effect of transplacentally acquired maternal antibody.[12]

Cell mediated immune responses are likely to be of considerable importance in recovery from infection as suggested by the severity of infection in patients with congenital T cell defects and by studies of cytotoxic T lymphocytes in animal models.[13] Unfortunately, ethical and technical difficulties in the collection of blood samples from infants have restricted the range of investigations and further studies of human infants are required to assess their ability to mount a cytotoxic T cell response and assess its relevance to the pathogenesis of infection.

Local responses in the respiratory tract

While it is clear that high concentrations of nasal antibody protect adult volunteers against RS virus infection[14] and stopping of virus shedding in the nasal secretions of infants coincides with the appearance of sIgA antibodies,[15] the effect of local immune responses on the pathogenesis of virus infection of the lung has not been established. Measurement of nasal responses may have little relevance to lower respiratory tract infection and we have failed to detect any discernible relation between concentrations of nasal virus and severity of chest infection in RS virus infected infants (unpublished results). Nasal secretions are, however, accessible and may give a picture of the general level of immunoresponsiveness in the infant.

Local, like systemic, responses are sluggish in the very young. This poverty of response may be particularly dangerous as nasal interferon[16] and IgM antibody responses in RS virus infected infants are considerably lower than those in infants of the same age infected with other respiratory viruses (unpublished results). Suppressed local responses may reflect the immunosuppressive abilities of RS virus described by Domurat[17].

Although these subtle defects may render young infants particularly vulnerable to RS virus infection, other factors seem to determine the outcome of individual infections, as neither nasal interferon nor secretory antibody responses correlate with disease severity (unpublished results). Welliver *et al*, however, report an association between early and high nasal anti-RS virus IgE antibody secretion and lower respiratory tract disease.[18] They have postulated that bronchiolitis results when a suppressor cell defect in RS virus infected infants leads to uncontrolled local IgE synthesis, degranulation of mast cells, and bronchoconstriction. Unfortunately, antigen specific IgE assays have proved difficult to establish elsewhere and these exciting results have not been confirmed in other laboratories.

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Archives of Disease in Childhood, 1987, **62,** 547–548

Lower limb deformity and prevention of scoliosis in cerebral palsy

Sustained motor delay, muscle imbalance, or restricted movement precede the musculoskeletal deformities which complicate many neuromuscular disorders. Infantile alignments, anteversion of the femoral necks, torsion of the tibia and coxa valga are retained,[1] and infantile postural asymmetry induces a structural asymmetry which lasts several years in normal children,[2] but persists as scoliosis, pelvic tilting, windswept deformity, and hip dislocation in those with neuromuscular disorders.[3] Spasticity and muscular hypotonia can coexist:[4] in the former muscle imbalance produces shortening, or contracture of the stronger muscles, elongation of the weaker muscles, and restricted joint movement. Hypotonia causes lax joints and flat feet.

Contractures seldom occur without hypertonia, and seldom present in the 11% of 'clumsy' children who have a previously unrecognised mild cerebral palsy[5] but are common in quadriplegics, with neurological signs and additional handicaps.[6] For those who teach themselves to stand before the age of 3 the prospects for walking unaided are good,[7] and only about 25% of the spastic and rigid contractures in this group require surgery,[8] usually of the calf and hip adductors.

Walking or potentially walking children

If adequate changes in posture (active or passive) and weight bearing (using a standing frame if necessary) are begun early the skeleton will be appropriately stressed. Improving quality and quantity of voluntary movement is not so easy because mobile children chose efficient, rather than normal looking, ways of moving and reserve their inefficient ways for visits to the clinic, this explains why their anteversion and other torsional abnormalities persist

A variety of splints and calipers have been devised which attempt to control leg posture and muscle imbalance without affecting mobility. Piedro boots (£37·00 to £43·00 depending on size) stabilise the flat rolled out feet which accompany hypotonia and persistent anteversion Medial sole and heel wedges (£3·00 each), possibly floated outwards (£5·00), may be added. A below knee outside iron (£34·00), round heel socket (£13·00), and inside T strap (£9·00) will support a lax ankle or counteract peroneal overactivity. Overaction or early contracture of calf muscles may be controlled by a 90° backstop to prevent plantarflexion of the boot If the foot is not dorsiflexed the child's heel remains high and produces a horizontal crease around the upper boot heel; an internal strap to restrain the heel is needed to hold the foot in place The plastic Ankle-Foot Orthosis (£80 00) is moulded to fit the contours of the calf, heel, and sole, and is worn under ordinary stockings and shoes to reduce plantarflexion and control foot posture (The prices quoted were current in December 1986.)

Serial below knee plastering to reduce established calf contracture was abandoned in the 1960s, as the force applied produced flat 'rocker bottom' feet Its use in treating equinus gait without contracture has continued,[9] and has been extended to treat early contractures and equinus postures. Controlled trials[10 11] have shown reduction in equinus lasting six months, with improved gait for up to one year.

Non-sedative muscle relaxants such as baclofen improve voluntary movement hindered by hypertonia,[12] and the new liquid formulation (5 mg/5 ml) permits fine adjustment of the dose in infants Relaxants may be used in conjunction with appliances to control hypertonia, but the combination of hypertonia, trunk and limb hypotonia, and weakness in many children means that results are unpredictable.

Mild hip adduction/internal rotation/flexion postures of the hips and flexion contractures of the knees are not easily influenced by small light appliances and are best tolerated provided they are neither worsening nor seriously interfering with free walking Passive hip abduction of less than 30° is one factor which starts spontaneous dislocation and must be dealt with surgically

Non-walking children

In severely handicapped children neither passive movement nor induced active movement can ever replicate the normal child's repertoire of daily movements, but they need frequent changes in posture to offset the continuous decerebrate or decorticate postures. Where little voluntary movement exists, appliances which maintain a posture at the expense of mobility are acceptable, and often take the form of special adaptations to the child's chair. Usually, the child's contractures are best dealt with surgically as poor trunk control is exacerbated by muscle relaxants, and without specific muscle relaxation or elongation there is little chance of maintaining alternative postures and thereby preventing future deformity.

Scoliosis, pelvic obliquity, and 'windswept hips' affect both hypotonic and hypertonic profoundly retarded children. Adducted hips dislocate first. The initiating postural asymmetry[13] can be controlled by a plagiocephaly helmet[14] and by plastic foam moulds, combined with early prone lying and symmetrical active movement treatment,[15] which should be begun in the first year before structural changes occur. Once these are present, the hip and pelvic position needs to be controlled by special chair adaptations, prone lying apparatus, standing frame, and wedged cushions between the knees, using a large towel as a sling to keep the adducted hip in abduction when lying supine both day and night. Adductor tenotomy or obturator neurectomy may be necessary to attain adequate abductions as this reduces the chance of posterior hip dislocation and improves sitting posture.

Apparatus which controls head, pelvis, and lower limb asymmetry also affects trunk postural mechanisms and thus deals with simple correctable (postural) scoliotic curves. Deteriorating, complex, and fixed curves, however, require the special clinical and orthotic expertise afforded by a scoliosis clinic.

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Original articles

Survival after balloon atrial septostomy for complete transposition of great arteries

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SUMMARY Mortality before surgery must be taken into account when comparing the surgical mortality of atrial redirection procedures (Mustard's or Senning's operation) and the arterial switch operation for patients with complete transposition. This is because the switch operation is usually performed within the neonatal period or early infancy but Mustard's or Senning's operation usually after 4 months of age. The outcome of balloon atrial septostomy was therefore assessed in all 102 infants with transposition of the great arteries (plus or minus associated anomalies) who underwent the procedure at our hospital in the 10 years from January 1975 to December 1984. We considered the procedure to have been unsuccessful if the patient died from any cause (including other surgical procedures) between the septostomy and subsequent interatrial repair (Mustard's operation) or arterial switch operation. Eighteen patients died, although in only two was this as a direct result of the septostomy.

Statistical analysis showed that low weight, presence of a persistent arterial duct, and coarctation of the aorta were significant risk factors. Early survival of infants with transposition of the great arteries has been dramatically improved after the introduction of balloon atrial septostomy.[1–3] Nevertheless, there is considerable attrition before definitive repair, which must be included in the prediction of overall outcome.[4–10]

After the description of Mustard's[11] and Senning's[12] operations for patients with complete transposition these surgical procedures became the standard treatment. They carry a fairly low operative risk[13] when there is an intact ventricular septum. Operative mortality and the risk of late complications are greater when there is an associated ventricular septal defect. The two operations are usually performed between the ages of 4 and 8 months, or later in patients with a ventricular septal defect who have had palliative pulmonary artery banding. The arterial switch[14 15] is now preferred in some centres, including our own. Because the arterial switch procedure is performed in the early neonatal period, when there is an intact ventricular septum, or during early infancy, when there is an associated large ventricular septal defect, mortality before definitive surgery is of paramount importance when comparing surgical results of atrial redirection or anatomic correction.

Patients and methods

Case records and catheter data of all infants with transposition of the great arteries who underwent balloon atrial septostomy at our hospital between January 1975 and December 1984 were examined. Only infants with atrioventricular concordance and ventriculo-arterial discordance were included. Thus those with an imperforate atrioventricular valve, absent atrioventricular connection, double inlet ventricle, common atrioventricular valve or double outlet right ventricle were excluded.

Of the 114 case records of infants admitted with transposition of the great arteries (up to December 1984), eight were excluded as septostomy was not performed. In six patients an arterial switch procedure was performed. Four are alive and well. Two of these patients, who had presented late to the hospital, died in the postoperative period aged 4·5 and 16 months. One patient, with a large secundum atrial septal defect, ventricular septal defect, and coarctation, did not require septostomy, had repair of coarctation of the aorta and pulmonary artery banding at 2 months, and is alive and well after Mustard's procedure at 5 months. The remaining child with intact atrial septum, ventricular septal defect, and left ventricular outflow tract obstruction is alive and well after systemic-pulmonary shunts at 3 months and 3·5 years As these patients did not undergo balloon atrial septostomy they were excluded from this study, which addresses the question of outcome after septostomy. Four were excluded because the case notes could not be traced, although catheter data were available. This left 102 cases in the study.

Balloon septostomy was considered to be a success if the patient went on to a definitive procedure (usually a Mustard's operation) and a failure if they died after the procedure but before an atrial redirection procedure or arterial switch procedure whether or not an atrial septectomy (Blalock-Hanlon operation)[16] was performed Actuarial analysis was used to investigate overall survival. Patients were withdrawn 'alive' on reaching definitive surgery.[9] Different variables were assessed retrospectively and the significance of each on survival was analysed using the Mann-Whitney U test and χ^2 test, as appropriate Each variable was examined separately, but this does not imply that, if interaction were to change this variable and no other, survival would necessarily be altered in the manner predicted.[10]

The variables evaluated were age, weight, haemoglobin concentration at the time of septostomy, the operator, time taken for the procedure, the use of prostaglandin infusion before septostomy, and the presence of associated anomalies. The latter included ventricular septal defect, persistent arterial duct, left ventricular outflow tract obstruction, and coarctation of the aorta. Ranges of values are shown in Table 1. The severity of left ventricular outflow tract obstruction was based on the gradient between left ventricle and pulmonary artery. It was regarded as mild if the gradient was less than 30 mm Hg and moderate to severe if higher. Gradients of up to 30 mm Hg may simply reflect excessive flow across a relatively normal left ventricular outflow tract.

Table 1 *Comparisons of variables in infants undergoing a successful or failed balloon atrial septostomy. Values are medians or No(%)*

Variables	*Successful operation (n=84)†*	*Unsuccessful operation (n=18)†*	*p Value*
Haemoglobin	14 50	13 80	NS*
Oxygen tension			
Before	4 00	3 50	NS*
After	4 90	4 90	NS*
pH			
Before	7 35	7 36	NS*
After	7 38	7 30	NS*
Duration of procedure (mins)	45 00*	37 50*	NS*
Age (days)	4 50	2 50	NS*
Weight (kg)	3 40	3 10	<0 05*
Ventricular septal defect	42 (50)	7 (39)	NS‡
Patent arterial duct	42 (50)	18 (100)	<0·01‡
Coarctation	7 (8)	4 (22)	<0·025‡
Left ventricular outflow tract obstruction	4 (5)	3 (17)	NS‡

NS=Not significant
*Mann-Whitney U test
†Incomplete data available for haemoglobin, oxygen tension, and pH
‡χ^2 test

Results

Of the 102 infants with transposition of the great arteries who underwent a septostomy during this period of study, 18 (18%) died before interatrial repair or arterial switch procedure (Table 2) Actuarial analysis of the data in Table 2 is illustrated in Figure 1 with confidence limits of 95%. All deaths occurred within six weeks of septostomy Of these,

Table 2 *Time intervals from septostomy, showing number of patients withdrawn from study each week*

Interval since septostomy (weeks)	*No of patients who died in this interval*	*No of patients withdrawn in this interval**
0–1	12	3
1–2	3	—
2–3	1	2
3–4	1	3
4–5	1	1

*Second column indicates patients withdrawn alive during this time for Mustard's operation

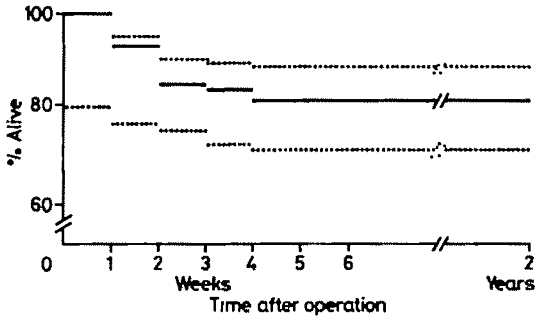

Fig 1 *Actuarial analysis of survival each week after balloon septostomy, with 95% confidence limits Patients were withdrawn 'alive' at the time of a corrective procedure Withdrawal of patients 'dead' includes only patients dying before a corrective procedure Deaths at surgery are not included. All patients had been subjected to a further corrective operation within two years of balloon atrial septostomy*

12 occurred within the first week and three within the second week of septostomy. There were 53 patients with complete transposition and intact ventricular septum. Ten of these (19%) died before 'corrective' surgery.

Low weight was the only measured variable that was considered to have a significant effect on outcome ($p<0·05$). The distribution of weight for success and failure (death) is seen in Figure 2. Histograms show a greater variance of weight in the group in whom septostomy was successful than in those in whom it was unsuccesful

The presence of a persistent arterial duct had a deleterious effect on survival ($p<0·01$). Coarctation was also a significant risk factor ($p<0·025$). The cause of death in the 18 patients who died before interatrial repair or arterial switch is shown in Table 3. Two patients died as a direct result of the procedure and one as a result of a tear of the tricuspid valve. The other patient had a ventricular septal defect and the catheter was inadvertently passed through the ventricular septal defect and into the left pulmonary artery. This was mistaken for a pulmonary vein. Attempted septostomy resulted in a tear of the ventricular septum with acute, complete heart block and death. At necropsy, the ventricular septum had been ruptured and the atrioventricular node bisected.

In three patients balloon atrial septostomy did not result in an adequate increase in arterial oxygen tension. Elective atrial septectomy was performed, but these patients died in the perioperative period. Four patients had an apparently adequate septostomy but died after subsequent repair of coarctation of the aorta. In no way was death directly related to septostomy, but their deaths still reflect attrition after this procedure. In our view, such patients must be included in the overall assessment of mortality.

The three patients who developed necrotising enterocolitis were all severely cyanosed and had developed a metabolic acidosis at the time of catheterisation. Whether or not enterocolitis would have developed in the absence of cardiac catheterisation and septostomy is not known. Inferior caval vein thrombosis with venous engorgement of the intestinal wall was not excluded in this group Other causes of death included meningitis and a cerebral infarct. It is not known if these illnesses were the direct result of cardiac catheterisation, and angiography or septostomy, or both.

The patient who arrested after septostomy was already severely hypoxic and acidotic before septostomy, and death may have been the inevitable outcome whatever was attempted. This also applies to the patient who died from aspiration and the infant with progressive acidosis after a technically adequate septostomy

It is of some encouragement to the cardiologist

Table 3 *Causes of death after balloon septostomy for the period 1974–1985 Total No of septostomies=102*

Post-repair coarctation ± persistent arterial duct ± pulmonary artery band	4
Necrotising enterocolitis	3
Attempted surgical septectomy	3
Cerebral infarct/meningitis	3
Cardiac arrest before septostomy	1
Aspiration	1
Severe acidosis	1
Tricuspid valve tear*	1
Ventricular septal tear*	1
Total	18

*Death directly due to septostomy

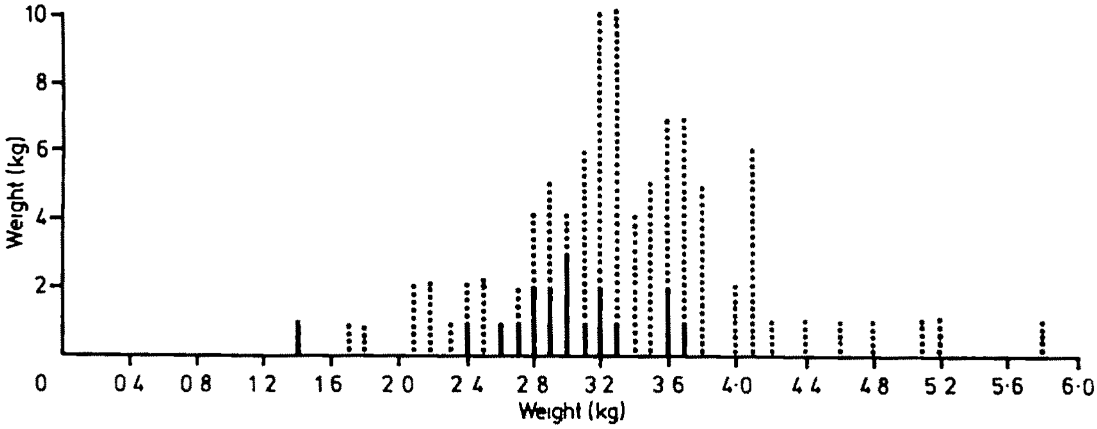

Fig 2 *Frequency distribution of weight at time of septostomy, success (dotted lines) and failure (continuous lines) are shown separately.*

that of the 18 deaths, only two occurred as a direct result of the procedure. The balloon atrial septostomies were performed by a total of nine different operators, and the two deaths both occurred after procedures by doctors in training, though they were supervised by a senior staff member.

Discussion

The same risk factors were evaluated in detailed analyses by Leanage *et al*[10] and Powell *et al.*[17] Our findings are in agreement with these studies and others in that coarctation and persistent arterial duct were found to be significant risk factors.[1 3 9 18 19] Analyses by Leanage and Powell also showed that age of septostomy, relative anaemia, the presence of a large ventricular septal defect, absence of left ventricular outflow tract obstruction, and pulmonary hypertension affected survival. These latter factors were found to be insignificant in our study. This may be attributed to the smaller number of patients and incomplete data for some variables Other studies have shown that cerebrovascular accidents and cerebral abscesses occur after septostomy,[20 21] as was seen in three of our patients.

Of note was that prostaglandin E_2 infusions did not significantly affect mortality. This may indicate that the condition of the patient before the balloon septostomy does not affect the subsequent result and no patient is too sick to benefit from the procedure.[22]

The outcome of balloon atrial septostomy should be considered along with that of Mustard's or Senning's operation or the arterial switch when considering overall survival. Although it is not the purpose of this paper to comment directly on the long term results of the various operations available, we have provided sufficient information for the hypothetical considerations of the surgical approach to treatment.

We have described the actuarial survival of infants with complete transposition after balloon atrial septostomy Most of the deaths occurred within two weeks and all within six weeks. As we have emphasised, in simple transposition of the great arteries the arterial switch procedure is performed at a younger age than Mustard's or Senning's operation. Mortality before surgery is therefore important when assessing surgical results. In patients with intact ventricular septum the neonatal switch operation is usually performed within the first two weeks of life. We do not know if this operation would have prevented all the early deaths after septostomy. It seems unlikely in that the causes of death included necrotising enterocolitis, acidosis, overwhelming infection, and cerebrovascular accidents, conditions that may have progressed to death irrespective of any therapeutic intervention. The time in which these patients were treated largely predated widespread adoption of the arterial switch procedure for transposition both with or without a ventricular septal defect For this reason Mustard's operation was the only corrective procedure considered in most patients.

Finally, in any hospital based series it is pertinent to ask whether the infants undergoing balloon atrial septostomy are representative of all children in the community with transposition of the great arteries[23] It is the policy of the paediatric cardiologists at our hospital to hold joint clinics with paediatricians in district general hospitals in the hope that such contact might facilitate early recognition and transfer of patients. We believe, therefore, that most children with transposition of the great arteries from such districts are referred and the data presented here are reasonably representative.[5] It must be remembered that the results of septostomy, as with any surgical procedure, will be improved if the sickest infants die before reaching hospital. Caution is still necessary, therefore, in comparing hospital based series with population based studies, although it is encouraging to note that the outcome of balloon septostomy has improved over the last decade.[9 10]

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Duodenal ulceration: review of 110 cases

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SUMMARY This paper describes 110 cases of childhood duodenal ulcer, which were diagnosed over 25 years: 63 were diagnosed by barium meal examination; 47 by upper gastrointestinal endoscopy. The mean age at diagnosis was 11·2 years, with symptoms reported in 46% before 10 years and in 15% before 6 years of age. There was often a considerable delay in diagnosis, particularly in the younger age group. Nocturnal pain (61%) and a close family history of duodenal ulcer disease (62%) were the most valuable pointers to the diagnosis. Fifteen children had required surgery for persistent symptoms. Thirty four had received treatment with an H_2 receptor antagonist, and all but four had had a satisfactory initial response. Seventy per cent relapsed within six months of discontinuing treatment, and long term maintenance treatment may therefore be necessary.

Recurrent abdominal pain is a common disorder in childhood, and it is well known that an organic disorder can be identified in only a minority of cases.[1] None the less, a small but significant number of these children have a peptic ulcer, usually in the duodenum.

The introduction of fibreoptic endoscopy to paediatric practice has permitted direct and accurate diagnosis of peptic ulcer.[2 3] The development of the H_2 receptor antagonists has facilitated medical management and so increased the importance of early diagnosis.

In the past 26 years a large number of cases of duodenal ulceration in childhood have been seen in the Newcastle area. In this report we review the experience gained in the diagnosis and management of these children. We suspect that the diagnosis may often be delayed, if not completely overlooked, especially in young children.

Patients

The case histories of 110 children with primary duodenal ulceration were reviewed. All had been seen in the 26 years between 1960 and 1985. They had attended either the Royal Victoria Infirmary, Newcastle upon Tyne, or the Queen Elizabeth Hospital, Gateshead, and each patient had been assessed personally by one of the authors.

Between 1960 and 1972 63 cases were diagnosed by barium meal examination. The diagnosis was accepted only if an ulcer crater could be shown, or if there was pronounced deformity of the duodenal cap and strong clinical evidence of active ulcer disease, such as haematemesis or melaena. Between 1973 and 1985 a further 47 cases were diagnosed by upper gastrointestinal endoscopy.

Results

Sex incidence. Of the 110 children, 87 were male and 23 female, a ratio of 3·8:1. This predominance of males agrees with that reported in other series.[4–6]

Socioeconomic groups. Cases were found in all socioeconomic groups, and when compared with the local population distribution, no excessive preponderance within any one group could be identified.

Family history. In 62% at least one first or second degree relative had had confirmed duodenal ulcer disease. The diagnosis had been established in all by radiology, endoscopy, or at surgery. The family incidence was sometimes highly impressive—for example, in the case of one boy two male siblings and the father were affected.

Age at onset of symptoms and at diagnosis. The mean age at diagnosis was only 11·2 years, and the children ranged from 4 to 15 years. Interestingly, symptoms were reported to have been present in 46% before the age of 10 and in 15% before 6 years of age. The mean interval from the reported onset of symptoms to the time of diagnosis was 1 8 years When symptoms began in early childhood the delay in diagnosis was likely to be considerably longer (Table 1). thus in those who were symptomatic by 6 years the mean interval to diagnosis was 4·8 years.

Clinical features (Table 2)

Abdominal pain occurred in 90% of cases and was a main presenting feature in 88% In 48%, however, it was not suggestive of ulcer dyspepsia. The pain was located in the epigastrium in only 51% of cases, while in 36% it was maximal in the central abdomen A temporal relation to meal times was described in only 52% of the cases Periodicity was a common feature, being present in 71%. Nocturnal pain was present in 67 patients (61%). If those who presented with gastrointestinal bleeding are excluded, whom, it is presumed, would have already been investigated, 80% of the remainder had nocturnal pain

Change in appetite was not a notable feature. Episodes of vomiting had occurred in 39%, but on each occasion this was accompanied by pain, and all had had previous episodes of pain

Epigastric tenderness was not usually a striking feature. Some degree of tenderness was noted in 54%, but its absence may relate to the state of activity of the disease at the time of examination.

A third of the children had an episode of haematemesis or melaena. Interestingly, this did not necessarily occur early in the illness; more than half had had symptoms consistent with peptic ulcer disease for at least a year before the episode of bleeding. As a presenting symptom upper gastrointestinal bleeding accounted for 36% of new cases in the 1960s This figure had fallen to 15% by 1979, almost certainly as a result of the policy of investigating larger numbers of children with abdominal pain No child in this series suffered a perforation of their ulcer

Two children have died, one as a result of an accident and one with Zollinger Ellison syndrome

Table 1 *Relation between reported age at onset of symptoms and delay in diagnosis*

Delay in diagnosis	*Percentage of cases*			
	<1 year	*1–2 years*	*3–5 years*	*>5 years*
Age at onset (years)				
2–5 (n=17)	0	20	30	50
6–9 (n=43)	7	41	48	4
10–13 (n=50)	42	44	14	0

Table 2 *Clinical features*

	Total No(%)		*Total No(%)*
Abdominal pain	99(90)	Vomiting	43(39)
Periodicity	78(71)		
Nocturnal pain	67(61)	Haemorrhage	36(33)
Tenderness	59(54)		
Dyspepsia	57(52)	Perforation	0(0)

Investigations

Radiology. Of the 63 cases diagnosed by barium meal examination, two thirds had a demonstrable ulcer crater. The remaining third had severe distortion of the duodenal cap, together with the clinical features mentioned previously.

Endoscopy. From 1973, all cases were confirmed by endoscopic examination From 1979, a deliberate change was made in the policy for selecting patients for investigation. in addition to those with a typical history suggesting peptic ulcer disease, and those with a history of gastrointestinal bleeding, children with recurrent abdominal pain who had had a history of nocturnal pain or a close family history of ulcer disease were also endoscoped This change in policy resulted in a three-fold increase in the number of endoscopies performed annually; but the number of duodenal ulcers detected also increased by a factor of three (Table 3). Fifteen per cent had multiple ulcers; duodenitis was present in 50%, 70% had obvious duodenal deformity and this was often severe and associated with scarring, suggesting long standing disease

Acid secretion studies. Studies of acid production had been performed in 26 children In seven of these betazole was used and in the remainder pentagastrin. Both of these agents produce comparable levels of acid secretion.[7] Maximal acid output varied between 0·05 and 1·17 mmol H^+/kg/hour (mean of 0·52) No control studies had been carried out. A study on 20 normal children aged between 2 and 12 years using pentagastrin reported a mean maximal

Table 3 *Effect of changing selection criteria for endoscopy*

	1973–78	*1979–85*
No of patients endoscoped	54	189
No of endoscopies/year*	9	27
No of duodenal ulcers detected	9	38
No of duodenal ulcers/year*	1 5	5 4
% of positive examinations	20	20

*Average number

acid output of 0·372 (SD=0·089) mmol H$^+$/kg/hour.[8] Nine of the 26 investigated here had results greater than 2 SD above this control mean.

Treatment

Until H$_2$ receptor antagonists were introduced children were treated by various dietary manipulations, antacids, and, in a few cases, propantheline or carbenoxolone sodium. Thirty four children had been treated with either cimetidine (25 mg/kg/day), or latterly ranitidine (150 mg twice daily) for eight weeks. Thirty (88%) had responded clinically to this initial course of treatment. As 70% relapsed within six months of discontinuing treatment, however, those who seemed to have had peptic ulcer disease for a prolonged period, judged by the history or the finding of severe scarring and deformity on endoscopy, were given an additional six month course of nocturnal maintenance treatment. Nevertheless, longer periods of maintenance were needed by some children. One boy received a total of four years of treatment. No child suffered any side effects.

Fifteen patients are known to have had surgery (Table 4). One of these was the patient with Zollinger Ellison syndrome. He was diagnosed before cimetidine had been introduced. Despite surgery, he succumbed to his illness. Of the remaining 14, two were lost to follow up in our department soon after surgery and no information is available on their subsequent course.

Ten patients were followed up for between two and 15 years postoperatively. Two of these, having failed to benefit from an initial vagotomy and pyloroplasty, required a second and more radical acid reducing procedure (partial gastrectomy). Another had a recurrence of his disease at the age of 23, seven years after surgery. Seven of these 10 had remained asymptomatic when last seen.

Follow up

Only 15 of the 110 children were followed up for more than 10 years in the paediatric department, and half of these continued to complain of symptoms when last seen. The long term outcome of the patients in this series is the subject of a study currently in progress.

Discussion

This is the largest reported series of duodenal

Table 4 *Details of subjects undergoing surgical procedures*

Case No	*Sex*	*Age (years) at diagnosis*	*Age (years) at surgery*	*Indication*	*Surgical procedure(s)*	*Postoperative follow up (years)*	*Outcome*
1	M	14	17	Recurrent pain and gastrointestinal bleeding	1 Vagotomy and pyloroplasty	2	Symptoms continued
			19	Recurrent pain	2 Partial gastrectomy		Unknown
2	M	12	14	Recurrent pain	Vagotomy and pyloroplasty		Unknown
3	M	14	14	Recurrent gastrointestinal bleeding	1 Vagotomy and pyloroplasty	3	Symptoms continued
			17	Recurrent pain	2 Partial gastrectomy	1	died (accident) at 18 yrs
4	M	8	8	Intractable pain and gastrointestinal bleeding (Zollinger Ellison syndrome)	1 Vagotomy and gastrectomy	<1	No improvement
			8	Vomiting, hypochloraemic alkalosis	2 Relief of duodenal adhesion and gastrectomy	2	Condition worsended
			10	Surgery to search for tumour	3 Unsuccessful exploration		Died shortly after surgery (hepatic ZE-tumour at pm)
5	M	10	17	Recurrent pain	Vagotomy and pyloroplasty	4	No recurrence
6	F	10	25	Recurrent pain	Vagotomy and pyloroplasty		Unknown
7	M	10	14	Recurrent pain	Partial gastrectomy	15	No recurrence
8	M	8	16	Pyloric stenosis	Vagotomy and gastroenterostomy	10	Symptoms returned 7 years after surgery
9	M	10	10	Intractable pain, melaena	Vagotomy and gastroenterostomy	5	No recurrence
10	M	11	16	Recurrent pain, melaena	Vagotomy and gastroenterostomy	7	No recurrence
11	M	12	12	Intractable pain, weight loss	Partial gastrectomy	4	No recurrence
12	M	9	12	Recurrent pain, and gastrointestinal bleeding	Vagotomy and pyloroplasty	8	No recurrence
13	M	10	13	Recurrent pain, duodenal stenosis	Vagotomy and pyloroplasty	1	No recurrence
14	M	12	14	Recurrent pain	Partial gastrectomy	1	No recurrence
15	M	11	13	Recurrent pain	Vagotomy and pyloroplasty	2	No recurrence

ulceration in childhood from a centre in Europe.[5 6 9–11] The published series from the North American continent and Europe suggest that large paediatric centres identify, on average, about two new cases annually, and rarely more than five.[12–17]

Between 1960 and 1972 one of the authors (RHJ) actively sought out cases from other hospital departments in the northern region, and this accounted in part for the large numbers seen in that period; no real comparison can therefore be made between the numbers at that time and subsequently. Neither is it possible to draw any conclusions about the local incidence of the disease.

Since 1973, however, the cases were all primary referrals. This was also the period in which paediatric endoscopy was introduced. The more liberal policy adopted in 1979 in selecting patients for investigation clearly had a strong impact on the numbers as the average annual detection rate rose from 1·5 to 5·4. The simultaneous decrease in the proportion presenting with overt gastrointestinal bleeding illustrates the fact that more of those being diagnosed in recent years have presented with abdominal pain rather than a complication of ulcer disease This is of considerable importance as studies have shown that one third of patients found to have a duodenal ulcer subsequently suffer an episode of bleeding, and with treatment the risk of this occurrence can be reduced.[18]

Paediatric duodenal ulcers are not, as is often assumed, only found in adolescents The onset may be in early childhood, as was seen in this series\ The young child is less likely to give an accurate description of symptoms, and this together with a reluctance to consider the diagnosis in younger patients probably explains the occurrence of the longest delays in diagnosis in this group.

It is important to realise that many of these children do not have the typical clinical pain syndrome of non-radiating epigastric pain, which begins several hours after eating, and is relieved by food, antacids, or vomiting. Many presented with recurrent central abdominal pain unassociated with meal times The high incidence of nocturnal pain in these children, however, is important: in Apley's series of recurrent abdominal pain only 7% of 118 children were woken at night by their pain.[1]

The high incidence of a family history of ulcer disease is striking Clearly the percentage of cases with an affected first or second degree relative will depend on factors such as the number of relatives. A genetic study was carried out by RHJ, in which 44 affected children and their families were matched with 35 control families. In the families with duodenal ulcers 8 2% of first and second relatives were affected, while in the control families only 1·9% were so affected; this illustrates the real importance of genetic factors.[19]

The optimal management of this disorder remains to be established. Clearly the H_2 receptor antagonists are effective in inducing a remission, as has also been shown in adults The high relapse rate following withdrawal of treatment, however, also follows the pattern reported in older patients.[18] The limited information available on the natural history of duodenal ulcer disease beginning in childhood suggests that the diathesis may quite often persist into adult life.[20] It may be that some patients will require protracted periods of treatment.

Considerable experience has now been gained in the use of the H_2 receptor antagonists, especially cimetidine. Healing rates, symptomatic responses, and the effectiveness of maintenance treatment with cimetidine and ranitidine seem to be similar.[21] Some rare specific side effects have been reported with cimetidine. It has been incriminated in cerebral and hepatic toxicity in children as well as in adults.[22 23] In male children gynaecomastia may develop.[24] Drowsiness and confusion have not been observed with ranitidine, and unlike cimetidine, it does not block androgen receptors, and gynaecomastia has not been reported.[24] It is important to realise that serious side effects are rare with either drug. Potential hazards must be balanced against the definite morbidity and mortality risks associated with surgery.

In conclusion, we suspect that awareness of the commonly atypical presentation of this disorder, especially in young children might result in earlier diagnosis. We wish to emphasise the importance of investigating those children with recurrent abdominal pain associated with nocturnal pain, or those who have a family history of peptic ulcer disease. Early recognition and treatment may reduce both morbidity and the incidence of complications.

Dr M S Murphy is an Action Research Training Fellow

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Two year study of cryptosporidium infection

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SUMMARY During a two year period 48 children admitted to hospitals in the Blackburn district were found to have cryptosporidium in stool samples. Cryptosporidium accounted for 6% of the 742 cases of childhood gastroenteritis, being as common as campylobacter. Altogether, 89% of children with cryptosporidiosis had diarrhoea, which was usually offensive and watery, and 80% vomited, the mean duration of both symptoms being six days. A substantial proportion were moderately ill with dehydration and persistent vomiting. Over half of all cases were aged 2 years or more and 37% were over 5 years. Most of the ill children were over 2 years, in contrast with other cases of gastroenteritis. Eight children were less than the 3rd centile for weight and three of these were investigated for failure to thrive. Only 6% of cases occurred in Asian children, but Asians accounted for 32% of all admissions with gastroenteritis and 59% of admissions with shigella. This unexpected ethnic difference may be due to limited contact with animals among Asians or to differences in diet.

Cryptosporidium is a protozoal coccidian parasite first identified in 1907 in the mouse and known for many years to be a cause of diarrhoea in calves. The first report of its association with gastroenteritis in man came 11 years ago,[1] and it is known to be a cause of severe intractable diarrhoea in immunocompromised patients.[2] In the last few years numerous epidemiological reports have shown cryptosporidium to be present in between 0·9%[3] and 7·2%[4] of faecal samples submitted to laboratories in the United Kingdom. Few reports, however, have detailed the clinical features in children admitted to hospital. An annotation stated that gastroenteritis due to cryptosporidium is mild, lasting up to two weeks, with four to five watery mucoid offensive stools a day, and often associated with vomiting, headache, and fever and abdominal pain in older children.[5] Of 27 cases who presented to a children's hospital, however, 52% were severe enough to require admission and 33% were dehydrated.[6]

This study attempted to ascertain the incidence, clinical features, and importance of cryptosporidium infection in children admitted to a district general hospital.

Patients and methods

The study group comprised all 48 children who were found to have cryptosporidium in faecal specimens during the two years 1 April 1984–31 March 1986 All children had been admitted to the paediatric wards of Park Lee Hospital, Blackburn Royal Infirmary, or Queen's Park Hospital, Blackburn, most of them with symptoms of gastroenteritis, prolonged diarrhoea, or failure to thrive. All faecal samples submitted to the district microbiology laboratory during the two years were examined for cryptosporidium oocysts. Smears of faeces on glass slides were stained by the saffranin-methylene blue technique[7] and examined by light microscopy. Concentration methods were not used. Oocysts of cryptosporidium were identified as spherical orange/pink bodies 4–6 μm in diameter, with evidence of more deeply staining internal structure.

Clinical details were ascertained retrospectively from the hospital case notes when cryptosporidium was identified. The total number of children with gastroenteritis was obtained from the district medical records department and numbers of other enteric pathogens from laboratory and ward record books and the district diagnostic index.

In a survey of 58 consecutive cases of cryptosporidium infection of any age identified by our laboratory on routine examination of stools submitted from April 1984–March 1985 details were requested of animal contact and consumption of raw unpasteurised milk The parents of 73 consecutive admissions with gastroenteritis to the children's infectious disease ward were also asked whether the family drank raw or pasteurised milk.

Statistical results were obtained using the χ^2 test.

Results

A total of 48 patients were identified, with ages between 11 days and 15 years. The boy:girl ratio was 1·6:1. Two patients, aged 11 days and 5 years, had no gastrointestinal symptoms and were analysed separately. The age distribution of the 46 remaining patients was compared with that of the 696 children with other causes of gastroenteritis admitted over the two years. Twenty five (54%) of those with cryptosporidium were aged more than 2 years compared with only 199 (21%) of those with other causes of gastroenteritis (p<0·001), and 18 (37%) were over 5 years. Only nine (20%) were less than 1 year of age compared with 429 (61%) of those with other causes of gastroenteritis admitted to our children's infectious disease ward (p<0·001). The duration of admission to hospital was one to 14 days, with a mean of 4·2 days. Eight patients (17%) stayed in hospital for seven days or more as a result of prolonged symptoms. In contrast, the mean duration of admission in 1985 of patients with non-bacterial gastroenteritis was three days, and only 5·5% of these stayed in hospital for seven days or longer. The mean duration of admission for salmonella was 4·2 days, for shigella 6·0 days, and for campylobacter 4·7 days.

Clinical features (Table 1). A total of 41 patients (89%) had acute diarrhoea, the duration of which ranged from two days to three weeks, with a mean of six days. In 27 of these patients (66%) the diarrhoea lasted more than five days and in eight (20%) more than 10 days. There was no significant difference in duration of diarrhoea at different ages. In most patients the diarrhoea was described as watery and often as very offensive. In two children, aged 2 and 3 years, respectively, there was a small amount of blood in the motions.

Altogether, 37 patients (80%) vomited for a duration of one to 15 days, with a mean of nearly six days. In 15 (40%) of these patients the vomiting lasted more than five days and in seven (19%) more than 10 days. Two patients vomited without any diarrhoea. One child with severe vomiting was constipated. Eleven (24%) were dehydrated (5% or greater). Of these, 10 were aged over 2 years and six over 5 years. Intravenous fluids were needed in 12 patients, all of whom were aged over 12 months. Ten of 25 children (40%) aged over 2 years were dehydrated and needed intravenous fluids compared with only two of 21 children (9%) aged under 2 years (p<0·01).

Fourteen children (30%) aged more than 1 year had definite abdominal pain, which lasted from one to 10 days. Eight children had fever, which was usually mild and lasted less than three days. Eight children had coughs that persisted for five to 14 days.

Table 1 *Acute clinical features related to age distribution in 46 children with cryptosporidiosis. Values are No of patients*

	Age group (years)			
	<1	*1–<2*	*>2*	*Total No*
Diarrhoea				
Total	7	11	23	41
Duration >10 days	3	1	4	8
Vomiting				
Total	6	10	21	37
Duration >10 days	2	2	3	7
Dehydration (5% or more)	0	1	0*	11
Intravenous fluid replacement	0	2	0*	12
Abdominal pain	0	4	0	14
Fever	1	1	6	8
Cough	1	0	7	8

*p<0·01

Failure to thrive

Eight children, aged 3 months to 5 years, presented with gastrointestinal symptoms and weight below the third centile. Cryptosporidium was found in stool specimens in all of these patients, including the three below who were investigated for failure to thrive.

Case 1. A 5 month old girl had chronic diarrhoea for 11 weeks with failure to thrive. She had a low one hour blood xylose concentration of 0·45 mmol/l but normal faecal fats and jejunal biopsy. Cryptosporidia were not seen on light microscopy of the biopsy specimen. She spontaneously recovered in the next month with a return to normal weight gain.

Case 2. A 16 month old girl had diarrhoea for six days and vomiting for 11 days. Weight was well below the third centile. The one hour blood xylose concentration was 0·3 mmol/l, improving to 1·33 mmol/l three weeks later, with resolution of her symptoms. Her weight slowly returned to the 10th centile over the next three months.

Case 3. A 16 month old boy presented with vomiting and an 800 g weight loss over one month without diarrhoea. The one hour blood xylose concentration was 0·7 mmol/l and light microscopy of jejunal biopsy specimen yielded normal results. He returned to normal weight gain in the next seven weeks without treatment.

In none of these three cases did investigation reveal any other cause for the failure to thrive and no other pathogens were identified

Neonatal infection. A 31 year old primigravida developed severe diarrhoea two days before the rapid delivery at home of a girl with birth weight of 1380 g and gestational age of 31 weeks. Cryptosporidium oocysts were found in the mother's stools and her diarrhoea continued for seven days post partum The mother visited her baby regularly after the first two days. The baby required ventilation for hyaline membrane disease for three days but thereafter did well and at no stage had diarrhoea or vomiting. Cryptosporidium occysts were identified in her stool three weeks after birth but were no longer present 11 days later No oocysts were identified in the mother's expressed breast milk, in nasopharyngeal aspirate from the baby, or in any other babies or staff on the unit. No other faecal pathogens were found in the mother or child.

Other pathogens. In association with the finding of cryptosporidium one child had a triple infection with giardia and campylobacter, having just returned from Pakistan. Three other children had dual infections, one with campylobacter, one with *Shigella sonnei,* and one with rotavirus. Two children had concurrent measles infection.

Seasonal incidence. The Figure shows the incidence by month of diagnosis There was an early autumn and a smaller spring peak.

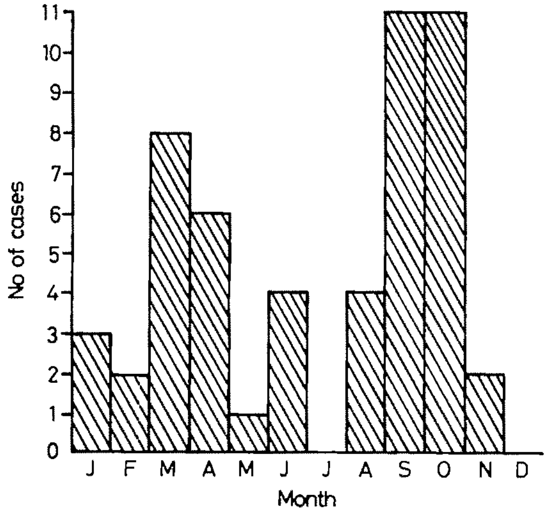

Figure *Seasonal incidence of cryptosporidium over two years by month of diagnosis.*

Table 2 *Comparison of cases of cryptosporidium gastroenteritis with cases with other causes of gastroenteritis, with reference in particular to the Asian population*

	Total No of cases	*% Total*	*No of Asians in each group*	*Asians as % of the total in each group*
Total	742	100	238	32
Rotavirus	162	22	42	26
Enteropathogenic *Escherichia coli*	47	6·3	12	26
Cryptosporidium	46	6·2	3*	6
Campylobacter	46	6·2	18	39
Shigella	34	4·6	20†	59
Giardia	27	3·6	12	44
Salmonella	23	3·1	8	35
Unspecified/other virus	357	48	123	34

*p<0·001, **p=0·001

Comparison with other causes of gastroenteritis. Table 2 shows the incidence of other major causes of gastroenteritis in the 742 children admitted to the district hospitals in the two years. The two children with cryptosporidium who had no bowel symptoms were excluded.

A significantly high percentage (59%) of children with shigella were of Asian origin (p=0·01), while only 6% of children with cryptosporidium were of Asian origin. Asians comprised about 22% of the child population, 28% of admissions to the children's infectious disease ward, and 32% of all admissions with gastroenteritis. The incidence of cryptosporidiosis in this ethnic group was unduly low compared with all Asian admissions with gastroenteritis (p<0·001)

The survey of 58 consecutive patients with cryptosporidiosis revealed that 31 of 54 responders (57%) regularly drank unpasteurised milk. This compared with 24 of 73 (33%) consecutive admissions of children with gastroenteritis (p=0·01). In addition, it was found that 32 of 53 (58%) of the patients with cryptosporidiosis had regular contact with pets or domestic animals. A study is in progress to ascertain the importance of this finding.

Discussion

This study confirms recent reports that have shown cryptosporidium to be a common cause of gastroenteritis. In our district it was as common as *Escherichia coli* and campylobacter and more common than giardia, shigella, and salmonella, findings that are similar to those from another hospital.[8] The age incidence in our cases admitted to hospital (37% over 5 years and only 20% under 1 year) contrasts markedly with that of children admitted with non-specific or viral gastroenteritis, who are usually infants. In our hospital 59% of all cases of gastroenteritis were in children less than 1 year. Laboratory surveys, however, show a greater proportion of cases of cryptosporidium in younger children.[9] The reason for the difference seems to be that cryptosporidiosis in the older child is more often unusually severe, necessitating admission to hospital. In the older children in our study admission to hospital was precipitated in most cases by severe and prolonged vomiting in addition to diarrhoea. A quarter of all our cases were sufficiently dehydrated to require intravenous fluids. Nearly all these children were aged over 2 years, and no infants under 12 months required intravenous fluids. In a smaller survey of 27 patients with cryptosporidiosis nine were dehydrated, and although there were few children aged over 5 years, only two of those dehydrated were aged less than 1 year.[6]

We feel certain that the older children in our study had more severe illness, but some admissions of older children could have been delayed because general practitioners do not expect dehydration in the older child. We do not know why the illness seems to be severer in older children. None of the children in our study showed any clinical evidence of immune deficiency.

Outside hospital, many cases are mild and even asymptomatic. In an outbreak in a day nursery in north-west England the rate of attack was seven of 13 children aged less than 3 years and 14 of 70 in the nursery overall (Riordan T. Personal communication.) None of the 14 required admission. Similarly, during a period of two months, 25 of 53 children at a day care centre in the United States had diarrhoea; cryptosporidium was found in 65% of symptomatic and 11% of asymptomatic children.[10] Asymptomatic excretion of oocysts is, however, generally rare in this country,[9] although it is common in India.[11] The mean incubation period after contact is six days,[12] and the shedding of oocysts generally stops within two weeks of the stopping of diarrhoea, though it may continue for longer in 15% of cases.[13]

The diarrhoea is typically very foul smelling and watery, such that our ward sister could suspect a case with some accuracy. Abdominal pain was quite common in the older children but fever only occurred in a small proportion. Headache was seldom prominent. Eight (24%) of our patients, nearly all of them aged over 2 years, had cough. Cryptosporidium is commonly found in the respiratory tract of fowls, and a recent report from Papua New Guinea described finding cryptosporidium in respiratory secretions from a child with acute diarrhoea and cough.[14] Respiratory symptoms are known to be common in other cases of gastroenteritis.

To document the full range of disease due to cryptosporidium infection, it would be ideal to search for oocysts in the stools of all children with diarrhoea and vomiting. This may not always be possible, however, in every district general hospital, and we recommend that a search for oocysts be made when a child aged over 1 year presents with prolonged watery offensive diarrhoea, severe or prolonged vomiting, and abdominal pains. The symptoms seem to be less specific in infants, but there may be failure to thrive with prolonged diarrhoea or vomiting. Failure to thrive has been reported previously,[15] with the cryptosporidial schizonts adhering to the intestinal mucosa on electron microscopy.[16] No abnormalities were seen on light microscopy in our two patients (cases 1 and 3) who underwent jejunal biopsy examination and had abnormal xylose absorption. Both recovered in a few weeks without treatment, but failure to thrive for several months has been reported[16] and it may now be advisable to look for cryptosporidium oocysts in the stools before more extensive investigation of a child with failure to thrive and chronic diarrhoea or vomiting.

The relative rarity of cryptosporidiosis in our Asian patients who were admitted to hospital was striking and unexpected and might be a valuable clue in assessing the importance of possible sources of infection. Asians, who are mainly Pakistani Moslems, make up about 22% of the child population and contribute an excess proportion of all cases of gastroenteritis, except for cryptosporidium. Cryptosporidium infection is common in developing countries, being particularly prevalent in children with diarrhoea in Liberia (7·9%),[17] Ghana (12·9%),[18] and India (13·1%),[11] although apparently it is often asymptomatic in infants under 6 months in southern India. Cryptosporidium is known to be zoonotic, causing diarrhoea in a wide range of domestic animals, and close contact with animals is normal in many developing countries. In Blackburn few Asians have any contact with animals and our Asian families do not keep pets.

In contrast, 32 of 55 (58%) patients with cryptosporidium in Blackburn had regular contact with pets or domestic animals. Some reports of cryptosporidiosis in country areas suggest animals as a source of infection,[19] although this association has not been confirmed in urban areas[9] where case to case spread seems to be more usual. Contact with pets, however, is extremely common—72% of the patients in the study from Bristol[9] and 58% in our survey—so it is difficult to obtain clear evidence of their importance as a reservoir of infection. The striking difference in incidence of cryptosporidiosis between Asians and non-Asians may indicate the importance of animals, and further work is needed to clarify this.

Dietary differences might account for the ethnic variation in incidence of cryptosporidiosis. A significantly greater proportion of our cases drank unpasteurised milk compared with children admitted to the ward without cryptosporidiosis, a result that contrasts with another study, which failed to confirm that raw milk is a source of infection. The Northwest and Yorkshire regions have the highest incidence of consumption of unpasteurised milk in the country.[20] We do not know the proportion of Asians who drink raw milk. Sausages[19] and tripe (Nichols G. Personal communication.) have both been implicated as possible sources of infection, tripe as a food for pets who may then infect their owners. Neither tripe nor sausages are eaten by our Asian population. A further possibility is of spread among day nurseries, but most cases seemed to be sporadic. Muck spreading and infected water[19] seem unlikely to be important factors in our patients, who mostly live in towns.

Finally, the association of preterm labour with an acute attack of cryptosporidiosis has not previously been reported. It is interesting that the baby remained asymptomatic despite her mother's quite severe illness, and the evidence points to cryptosporidiosis being less pathogenic in young infants than in older children The mode of transfer of cryptosporidium from mother to child was not ascertained with certainty, but further spread in the special care nursery was probably prevented by the strict infection control procedures that normally operate there.

We thank the nursing staff of ward 1, Park Lee Hospital, the microbiology staff at Blackburn Royal Infirmary, and Drs Jivani and Fossard for helpful criticism and permission to report their patients

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Comparison of four pancreatic extracts in cystic fibrosis

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SUMMARY Four different pancreatin products, Pancrease, Creon, Pancrex V Forte, and Pancreatin Merck, were compared in a random crossover trial in children with cystic fibrosis. The results of our study showed that patients who received Creon and Pancrease had fewer gastrointestinal symptoms than patients who received Pancrex V Forte and Pancreatin Merck. Fat absorption was significantly improved with Pancrease when compared with Pancrex V forte and Pancreatin Merck. Also the fat absorption with Creon was superior to that with Pancrex V Forte There was no significant difference in fat absorption between Pancrease and Creon, Pancrex V Forte and Pancreatin Merck, or Pancreatin Merck and Creon. Faecal nitrogen content was less with both Creon and Pancrease compared with Pancreatin Merck.

Creon and Pancrease allow the patient with cystic fibrosis to take a high energy diet without any dietary restrictions.

Pancreatic insufficiency occurs in most patients with cystic fibrosis.[1] Supplementation with adequate doses of pancreatic extracts decreases the number and bulk of stools and improves growth.[2–4] There is, however, a great deal of variability between the different preparations and patients' responses to them. The older preparations have been shown to provide less than 3% of ingested lipase activity at the ligament of Treitz as a consequence of acid/pepsin digestion in the stomach[5] Recent studies have shown that a microsphere system of delivering enzyme preparations significantly enhances fat absorption compared with conventional enzyme preparations.[6–8] The microsphere are administered in a gelatin capsule that dissolves in the stomach. The pancreatin in the released microspheres is protected from acid/pepsin digestion by a pH sensitive coat that does not dissolve until the pH exceeds roughly 5·5. Thus the granules mix with the gastric contents and enzymes are not released until the pH of the chyme exceeds 5·5 within the duodenum In this study we compared the efficacy of Pancrex V Forte tablets (Paines and Byrne) with three microsphere systems—namely, Pancrease (Ortho-Cilag), Creon (Duphar), and a new pancreatin product, Pancreatin Merck (Merck Pharmaceuticals) (Table).

Patients and methods

Patients. Nineteen patients who were currently receiving treatment at our unit were enrolled in the study. Their median age was 12 years 1 month, with a range of 6 years 2 months to 20 years 1 month, and their most recent Shwachman clinical scores and Chrispin Norman *x* ray scores were 80 (60–95) and 6 (0–21), respectively All children had symptoms of cystic fibrosis and all had had at least two raised sweat sodium and chloride concentrations. At the time of entry into the trial all patients were on an unrestricted normal diet that contained a median of 3·14 (1·38–4·48) g of fat/kg/day and were receiving as their pancreatic supplement a median of 18 (6–40) capsules of Pancrease each day

Table *Enzyme content of the four different preparations used in the study*

Preparation	*Manufacturers*	*Enzyme content per tablet/capsule (BP units)*		
		Lipase	*Amylase*	*Protease*
Pancrex V Forte	Paines and Byrne	5600	5000	330
Creon	Duphar	8000	9000	210
Pancrease	Ortho-Cilag	5000	2900	330
Pancreatin	Merck	7700	10 000	650

Study design. (Fig. 1). The study in each patient was undertaken over seven weeks. During the initial run in, a seven day dietary assessment was undertaken to determine the average daily fat intake. The patients and parents were instructed about the principles of a constant fat diet and during weeks 1, 3, 5, and 7 the parents weighed and recorded each portion of food to ensure a constant daily fat intake, the amount of fat taken being similar to the normal fat intake of their child Although we did not use a constant protein diet, we assessed the protein intakes of five patients during the four study weeks of the trial. These were all well controlled and for this reason dietary protein assessment was not undertaken in the other patients. The dietary management was closely supervised by a paediatric dietitian (AM)

Pancreatic extract was given during the study as follows In week 1 the patients continued to take their usual amount of Pancrease each day, ensuring the same daily total number of capsules. The patients were then randomly assigned to fortnightly treatment periods with Pancrex V Forte, Creon, and Pancreatin Merck. The dose of pancreatic extract was so adjusted that during each treatment fortnight the daily lipase content was identical to that received when on treatment with Pancrease.

Stools were collected over 48 hours at the end of weeks 1, 3, 5, and 7. Faecal fat content was measured using the method already described[9] and faecal nitrogen using a Tecator Kjeltec Auto Model 1030 nitrogen analyser. This timing of collection was chosen to minimise disturbance to schooling and work. The daily output of faecal fat and nitrogen was calculated from the 48 hour faecal collection.

Throughout the investigation the patients recorded daily their subjective symptoms (on a scale of 1–3) for abdominal distension, stool odour, stool consistency, and also the number of bowel actions each day. For the purpose of analysis, the symptom scores were taken from the second week of treatment when the patients were on a constant fat diet. Some patients were not able to tolerate one particular preparation and in these cases the weekly symptom score was estimated from the daily scores available before stopping that preparation At the end of the study each patient was asked for their own individual preference of pancreatic extract All results are expressed as median (range).

Statistical analysis was undertaken using Wilcoxon's rank sum test and Student's paired t test where appropriate. Consent for this study was given by the local ethical committee.

Results

Six patients were unable to tolerate the Pancrex V Forte because of untoward gastrointestinal symptoms of steatorrhoea, and in five of these patients faeces were not collected as the patients were not on the constant fat diet, thus there were only 14 faecal fat and nitrogen estimations in the children taking Pancrex V Forte. There was excellent dietary

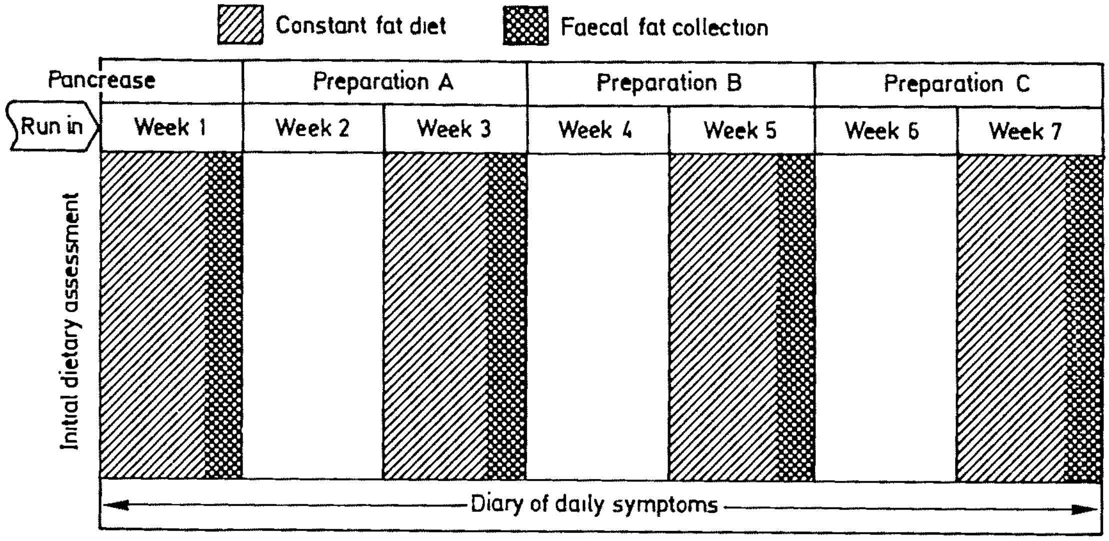

Fig 1 *Outline of study design of four pancreatic extracts in patients with cystic fibrosis*

recording by the patients with very little variation in dietary fat intake in each study period.

Weekly symptom score. (Fig. 2). There was no difference in the weekly symptom score when on Pancrease (38 (22–57)) and on Creon (40 (9–54)), but both were significantly lower (p<0·01) than the symptom scores for Pancreatin Merck (55 (20–75)) and Pancrex V Forte (62 (40–78)). There was no significant difference for the scores between Pancrex V Forte and Pancreatin Merck.

Fat absorption. (Fig 3). There was no difference in the per cent fat absorption between Pancrease (87 (24–95)) and Creon (85 (56–94)), but both were significantly higher however, than Pancrex V Forte (74 (52–93)) (p<0 01), and Pancrease was significantly higher than Pancreatin Merck (81 (34–94)) (p<0·05). There was no significant difference between Pancrex V Forte and Pancreatin Merck nor between Pancreatin Merck and Creon.

Faecal nitrogen. (Fig. 4). There was no significant difference in the faecal nitrogen content between Creon (2·1 (0·6–4·4) g/day) and Pancrease (1·6 (0·5–8·6) g/day) and between Pancrex V Forte (2·9 (0·4–5·4) g/day) and Pancreatin Merck (2·7 (1·0–

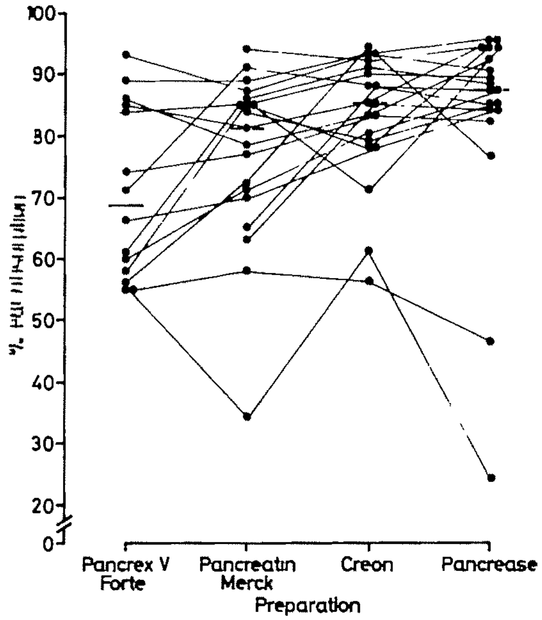

Fig 3 *Fat absorption, as derived from (dietary fat–faecal fat)/dietary fat×100%, in patients with cystic fibrosis treated with four pancreatic extracts. The horizontal bar represents the median value*

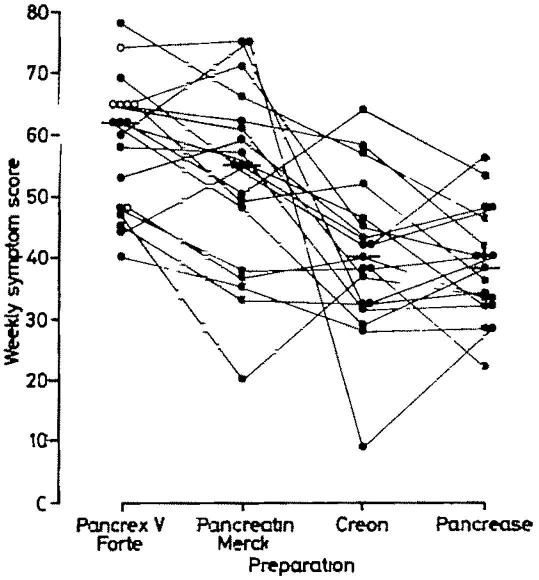

Fig. 2 *Weekly symptom scores for patients with cystic fibrosis treated with four pancreatic extracts The horizontal bar represents the median value. Open circles represent six patients unable to tolerate Pancrex V Forte because of undue symptoms.*

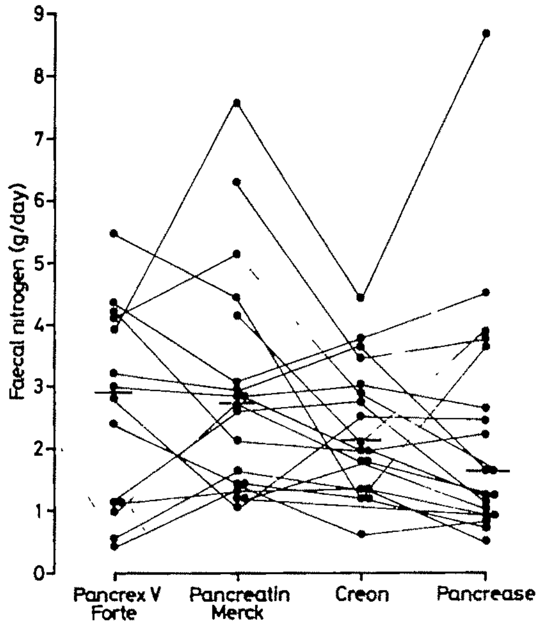

Fig. 4 *Faecal nitrogen content (g/day) in patients with cystic fibrosis treated with four pancreatic extracts. The horizontal bar represents the median value*

7·6) g/day). The only difference noted was that both Creon and Pancrease were significantly lower than Pancreatin Merck ($p<0·05$).

On subjective questioning, eight children preferred Pancrease as it was the preparation they were accustomed to using, 10 children preferred Creon as it was equally efficacious as Pancrease but fewer capsules had to be taken, and one preferred Pancrex V Forte as he liked the taste. No patient stated a preference for Pancreatin Merck.

Discussion

In this study we have confirmed the benefits of the microsphere system of pancreatic extract. Previous reports have already shown the superiority of Pancrease over conventional preparations.[6–8] Clinical evidence of the effect of Creon has to date only appeared in German publications.[10 11] This study shows that patients on Creon and Pancrease had fewer gastrointestinal symptoms than patients on Pancrex V Forte and Pancreatin Merck. Fat absorption was significantly improved with Creon and Pancrease compared with Pancrex V Forte, and also the fat absorption with Pancrease was superior to that with Pancreatin Merck, although Pancreatin Merck and Creon were similar. Faecal nitrogen content was less with both Creon and Pancrease compared with Pancreatin Merck. When taking either Creon or Pancrease children with cystic fibrosis were able to enjoy a normal diet without any dietary fat restrictions. Moreover, dietary fat absorption was well over 80% in most patients and 90% in one third of the children, reflecting the high efficiency of these two products Our results with Pancreatin Merck were less satisfactory than with Creon or Pancrease and were similar to Pancrex V Forte. Pancreatin Merck is of similar formulation to Creon and Pancrease

Creon and Pancrease have revolutionised the dietary management of patients with cystic fibrosis. It has long been recognised that good nutrition is of paramount importance in the host who has chronic infections [12–14] Hyperalimentation in children with cystic fibrosis has been shown to be associated with improvement in pulmonary function.[15] Fat as a major energy source in the diet is now freely available to children with cystic fibrosis since the availability of more effective pancreatic supplements. Optimum nutrition, without dietary restriction, is thus possible in the child with cystic fibrosis.

There are other advantages of the microsphere system preparations. All but one patient preferred the taste of the new preparations and because of their increased efficiency the children found that fewer capsules were required to control gastrointestinal symptoms Many patients reported a greater sense of 'well being' with Pancrease and Creon because of lack of symptoms. Several children preferred Creon to Pancrease because the increased enzyme content of Creon meant that they took fewer capsules. Comparative costs showed that in this study Creon was 40% cheaper than Pancrease, though both products were four to seven times more expensive than Pancrex V Forte. It must be remembered, however, that on the dose of Pancrex V Forte used in this study six patients had uncontrollable symptoms and dietary malabsorption was common; thus a larger dose of Pancrex V Forte would be necessary to control symptoms, with the possible dangers of hyperuricaemia[16] and hyperuricosuria.[17] On such a larger dose of Pancrex V Forte the price differential between Pancrex V Forte and Creon and Pancrease would not be so pronounced.

We conclude that both Creon and Pancrease are equally effective in correcting and controlling the symptoms of pancreatic insufficiency in children with cystic fibrosis. We believe that one or other of these two products is currently the treatment of choice when pancreatic supplementation is used.

We thank the parents and patients for help in this study, Merck Pharmaceuticals, Duphar Laboratories, Ortho-Cilag Ltd, and Paines and Byrne Ltd for financial support, and Mrs C Silburn for secretarial help MPW is supported by a grant from the Cystic Fibrosis Research Trust

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Efficacy of varicella vaccine in patients with solid tumours

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SUMMARY Thirty nine children with malignant disease and without antibodies to varicella zoster virus were immunised with a live Oka strain varicella vaccine. Seroconversion was shown in 24 of those who were vaccinated but five of 18 who responded to the vaccine who were followed up for over six months subsequently lost their antibodies. Of 10 children who were revaccinated, nine responded to the second dose but three lost their antibodies within six months to two years. Four children developed reactions related to the vaccine, one local and three generalised, but all these were transitory and of no clinical concern. Nine of those who were vaccinated, including four who did not respond to the vaccine, have subsequently had close exposure to varicella but none has developed the disease.

Varicella is usually a mild disease that is rarely associated with serious complications. The important exception to this is when the disease occurs in those who are immunocompromised. In these circumstances the infection may disseminate to organs such as the lungs and brain and has been associated with mortalities ranging from 7% to 30%.[1,2] In 1974 Japanese workers described the development of a live varicella vaccine,[3] and this was soon followed by a further report that the vaccine had been safely administered to children with leukaemia and other malignant diseases.[2] Vaccines derived from the original Japanese Oka strain of varicella zoster virus have since been administered to various groups of children at risk from complications of varicella in trials carried out in both Japan and the United States.[4-6]

We report our experience with one of these vaccines administered to children with malignant disease

Patients and methods

Patients. Children seronegative for antibodies to varicella zoster virus were selected for vaccination from patients who were attending the paediatric oncology clinic at our hospital. The underlying malignancies in these children are shown in the Table.

The vaccine was not given to children with disseminated disease or to those whose lymphocyte count was less than $1{\cdot}2\times10^9$/l. Informed consent was obtained from the parents of all the children before vaccination was undertaken and the study was approved by the ethical committee of our hospital.

Vaccination. The Smith Kline-RIT live Oka strain of varicella vaccine was kindly provided by Dr F Andre (RIT, Rixensart, Belgium). A single 1 ml dose of the vaccine, containing not less than 1000 plaque forming units, was administered subcutaneously. Some children were vaccinated on completion of treatment for their disease, whereas others were given vaccine between courses of chemotherapy. In either instance vaccine was not given until 10 days had elapsed since the last treatment and treatment was not started until at least 10 days had elapsed after vaccination.

Table *Malignancies in 39 patients given live varicella vaccine*

Rhabdomyosarcoma	9
Wilms' tumour	9
Non-Hodgkin's lymphoma	4
Ewing's tumour	3
Acute lymphocytic leukaemia	3
Central nervous system tumour	2
Nasopharyngeal carcinoma	2
Yolk sac tumour	2
Osteosarcoma	2
Histiocytosis	1
Renal carcinoma	1
Acute myeloid leukaemia	1
Total	39

Follow up. Blood samples were taken routinely, from each patient before vaccination and five weeks after vaccination for evidence of seroconversion. Thereafter, blood samples were taken at each attendance at the clinic to determine the longevity of any induced humoral response. Parents were asked to report immediately any reaction to the vaccine and at each attendance at the clinic they were questioned carefully about any exposure to varicella.

Serology. Serum samples before and after vaccination were tested for antibodies to varicella zoster virus by complement fixation and radioimmunoassay procedures that have been described previously[7,8]

Results

Serological response to the vaccine. To date 39 seronegative children have been vaccinated, and 24(62%) seroconverted within five weeks of vaccination. The antibody titres after vaccination have shown considerable individual variation, ranging from <4 to 512 (median:8) by complement fixation and 100 to >25 600 (median 3200) by radioimmunoassay. Antibodies in four patients were detectable only by radioimmunoassay and not by the less sensitive complement fixation test. One of these patients had received zoster immune globulin because of exposure to varicella three days after vaccination, so the antibodies detected may not have been induced by the vaccine.

Interestingly, three of those who were vaccinated who had not initially seroconverted were later found to have developed antibodies to varicella zoster virus. Two of these were found to have good antibody titres six and 11 months, respectively, after vaccination and both had been exposed to varicella in the interval between the tests. Neither had developed any symptoms suggestive of varicella. The third patient was negative two years after vaccination but when retested at 3 years had antibody titres of 128 by complement fixation and >25 600 by radioimmunoassay. There was no known exposure to varicella nor any symptoms suggestive of varicella during this period.

Reactions to the vaccine. Only four (10%) of the children showed any reaction to the vaccine. Three patients developed very mild varicella about three weeks after vaccination, from which they rapidly recovered. The fourth child developed a small crop of vesicles at the inoculation site, which during the next few days became surrounded by a reddened indurated area of skin, 5 cm in diameter, with a necrotic centre (Fig. 1). This local lesion developed three weeks after vaccination and healed within seven days. These children with clinical reactions interestingly developed the highest antibody responses, comparable with those after wild virus infection.

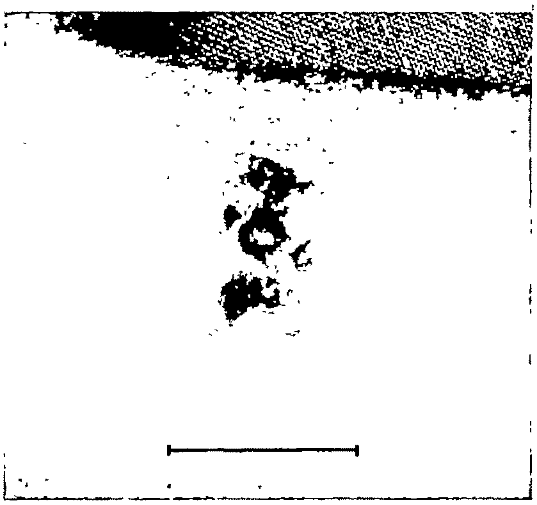

Fig 1 *Local reaction at the inoculation site on the right upper arm in a recipient of the live varicella vaccine. Bar is 5 cm in length*

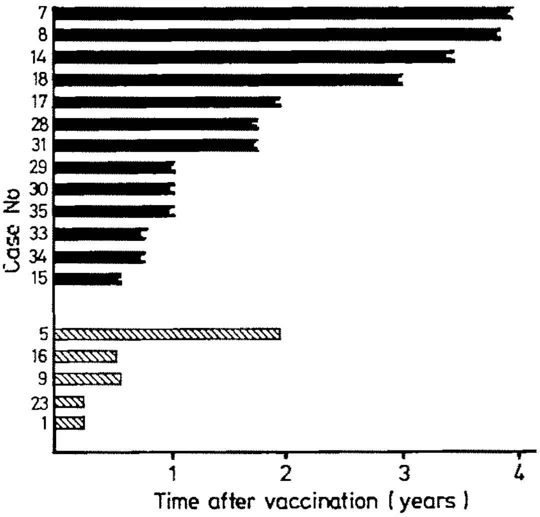

Fig 2 *Duration of immune response in patients who initially responded to vaccination. Solid bars represent patients with persisting antibody, hatched bars represent those who have lost their antibodies*

Longevity of the humoral immune response. So far 18 of the 24 patients who developed antibodies after vaccination have been followed up for more than six months It was not possible to obtain comparable data on the other patients because of death due to malignancy, recent vaccination, or loss to follow up Figure 2 shows that 13 (72%) of the 18 patients still had detectable antibody titres in all serum samples that were tested during intervals that ranged from six months to four years. The remaining five patients lost their antibodies after periods ranging from six months to two years.

There was no definite correlation between duration of antibody response and initial antibody titre after vaccination. One of the patients who had a vaccine reaction (case 5) developed one of the highest antibody titres initially but lost the antibodies by two years

Protection. Altogether, nine of those who were vaccinated experienced close (home or playmate) contact with varicella. Five of these were patients who did respond to the vaccine and four who did not. None developed clinical varicella, although one of the responders showed a considerable rise in antibody titre after contact and two nonresponders seroconverted. It was of interest that two siblings of one of those who was vaccinated had had contact with the same index case and both developed varicella.

Revaccination. So far 10 children have been revaccinated six to 12 months after their first doses, five because of poor and waning initial responses and five who did not respond. Nine of these children responded to the second dose, but on follow up three (33%) had lost their antibodies six months to two years after revaccination Four children remained positive for at least one to three years.

There was no correlation between the responses after the first and second doses. None of those who were revaccinated has shown clinical responses.

Discussion

This investigation with the live Oka strain varicella vaccine encourages us to believe that it is of prophylactic value for children who are being treated for malignant disease. The few reactions observed in children with solid tumours were mild and of little concern to attending physicians. This is consistent with the observations made in trials of this vaccine in children with leukaemia.[9] Immunocompromised children who react to this attenuated vaccine may be those that would have experienced the severe, perhaps fatal, forms of varicella had they been infected with wild strains

The antibody responses to the vaccine were generally inferior to that observed after wild virus infection in normal children. This is, of course, a general feature of attenuated vaccines and could be expected particularly when administered to immunocompromised patients whose ability to produce antibody may be impaired Indeed, one of our seronegative patients developed typical varicella, fortunately without complications, before she had been vaccinated. Three weeks after onset her antibody titres by complement fixation and radioimmunoassay were only 4 and 600, respectively, and no antibody could be detected by either method in a serum sample taken a year later. Furthermore, one of the children who did not initially respond to the vaccine but seroconverted after contact with varicella lost the antibodies within nine months. The level of immune responsiveness in the recipient affects the seroconversion rate after vaccination.[9] Thus the immunosuppressed state of our vaccines with solid tumours probably accounts for the considerably lower seroconversion rate (61%) observed, compared with the rate in excess of 90% reported in healthy recipients.[9]

Despite the poor humoral response, the vaccine seems to confer good protection. Nine of our patients who were vaccinated were subsequently exposed to varicella and none (<11%) developed the disease, although some may have had subclinical infection, which may explain the delayed but high antibody responses occasionally observed. In a large study, however, involving 192 children with leukaemia, 4% of those who were vaccinated who received one dose of vaccine subsequently developed varicella.[6] These findings should be compared with the expected infection rate in susceptible children of at least 80% after close contact. The apparent protective effect even in patients with poor antibody responses shows the difficulty in determining immune state in immunocompromised patients. Even a sensitive antibody test such as radioimmunoassay may still be inadequate for showing immunity in these patients, and a test for cellular immunity —for example, lymphocyte transformation[10]—may be more suitable.

As a result of the unsatisfactory antibody response in some of our children we have begun revaccinating those who either failed to seroconvert or who no longer have detectable antibody We are encouraged by our early results with this new regimen in that nine of 10 patients who have been revaccinated have developed good antibody responses, although three have subsequently lost their antibodies again. Clearly, further studies are required to determine the optimum immunisation schedule in these patients.

We believe that sufficient evidence about varicella vaccine has now been accumulated over the past 10 years,[9] regarding its safety and efficacy, to recommend its wider use in patients at risk of developing the severe complications of varicella.

We acknowledge the help of Dr A Smith and Miss V Potter with this study

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Acute lymphoblastic leukaemia: trimethoprim resistant organisms during treatment

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SUMMARY A cross sectional study was carried out in children receiving treatment for acute lymphoblastic leukaemia to determine the prevalence of trimethoprim resistant organisms in their gut flora and to compare this with a control population. There was a significantly higher prevalence of trimethoprim resistant bacteria in the study group (61%) compared with controls (14%). A longitudinal study showed that emergence of these organisms was intermittent during treatment.

Children receiving chemotherapy for acute lymphoblastic leukaemia are at increased risk of infection by *Pneumocystis carinii.* A combination of trimethoprim and sulphamethoxazole, co-trimoxazole, has proved useful in preventing such infecions[1] and is now included in the treatment protocol for acute lymphoblastic leukaemia. Co-trimoxazole has been used in an attempt to decrease numbers of enterobacteriaciae in faeces of adults and children receiving chemotherapy for leukaemia and to prevent bacterial infection.[2–5] Recently, such regimens have been associated with an increased intestinal colonisation by trimethoprim resistant coliforms, and several patients have developed serious infection with these bacteria.[6 7] A further complication is that resistance to both trimethoprim and sulphamethoxazole can be encoded on plasmids, and these plasmids may also code for resistance to other antimicrobials, including gentamicin, ampicillin, and chloramphenicol.[8] Thus administration of co-trimoxazole may select for bacteria resistant to many antimicrobials. Although the emergence of bacteria resistant to trimethoprim in adults with leukaemia who are receiving long term co-trimoxazole is well documented,[2] there is little information available for children We present the results of a year's prospective survey into the prevalence and incidence of trimethoprim resistant coliforms in children with acute lymphoblastic leukaemia receiving long term co-trimoxazole.

Patients and methods

All patients attending the regional oncology unit, Alder Hey Children's Hospital, for treatment of acute lymphoblastic leukaemia were entered into the survey. Nasal swabs, throat swabs, and faeces were inoculated on to Direct Sensitivity Test agar (Oxoid Ltd, Basingstoke), incorporating 7% (vol/vol) lysed horse blood and trimethoprim (4 mg/l), and incubated aerobically at 37°C for 18 hours. Colonies growing on the selective plate were identified using standard techniques and their susceptibility to a series of antibiotics was determined using a controlled disc diffusion method.[8] Minimum inhibitory concentrations were determined using an agar incorporation method, as described previously.[9] The survey was designed in two parts.

Firstly, a cross sectional survey was carried out to determine the prevalence of trimethoprim resistant aerobes in the intestinal flora of all children receiving chemotherapy for acute lymphoblastic leukaemia. Specimens were collected over two weeks when children were attending as outpatients. This was compared with the prevalence of carriage of trimethoprim resistant bacteria in the faeces of 568 children who were not receiving co-trimoxazole.

Secondly, a longitudinal study was carried out on children presenting with acute lymphoblastic leukaemia for the first time. Specimens were obtained before induction and at the beginning of prophylaxis and thereafter at monthly intervals. Three patients received co-trimoxazole daily and the remaining patients thrice weekly, at dosages of trimethoprim 160 mg/m^2/day and sulphamethoxazole 800 mg/m^2/day.

Statistical analyses were performed using χ^2 test with Yates's correction for small numbers where applicable.

Results

In the prevalence study trimethoprim resistant bacteria were not isolated from the anterior nares or throats of any children nor were trimethoprim resistant Gram positive bacteria isolated from any site. Of 41 children who received prophylaxis with co-trimoxazole, 25 (61%) were excreting trimethoprim resistant bacteria in their faeces. In contrast, significantly fewer ($p<0.001$) of the control children (79 of 568, (14%)) were excreting trimethoprim resistant bacteria. All isolates obtained were Gram negative. A greater variety of trimethoprim resistant bacteria were obtained from the control group, but *Escherichia coli* was the predominant isolate in both groups (Table 1). All the resistant bacteria had minimal inhibitory concentrations of greater than 800 mg/l trimethoprim. Twenty four (96%) of the trimethoprim resistant bacteria specimens isolated from the study group were also resistant to sulphamethoxazole, whereas 65 (82%) of those obtained from the control group were similarly resistant. None of the isolates obtained from the study group was resistant to gentamicin or tobramycin, but 22 (88%) were resistant to streptomycin and spectinomycin. Twenty three (92%) of the trimethoprim resistant bacteria from the study group were also resistant to ampicillin and ticarcillin and 77 (97%) of those from the control group were similarly resistant.

Thirteen children were entered into the longitudinal study. Two of the children (15%) were already excreting trimethoprim resistant strains of *E. coli* before they received chemotherapy (Table 2). They both continued, intermittently, to excrete trimethoprim resistant *E. coli* of the same biotype as the original isolates. One child also excreted a trimethoprim resistant strain of serratia on a single occasion. Seven patients (54%) who were surveyed for a total of 22 months did not acquire trimethoprim resistant bacteria. Five of these patients were followed up for only one to two months. Of the four patients (36%) who acquired resistant bacteria, only one had acquired them by the second month, two by the third month, and one by the fourth month. Once colonisation had occurred, it did not follow that the patient continued to be colonised; indeed, intermittent excretion of resistant bacteria was the rule. There was no difference in risk of acquisition of resistant bacteria between children receiving daily or thrice weekly co-trimoxazole

Table 1 *Trimethoprim resistant bacteria isolated from faeces in 41 patients and 568 controls*

Bacteria isolated	*Study group*	*Control group*
Escherichia coli	22	51
Proteus	2	8
Citrobacter	1	1
Klebsiella	0	11
Acinetobacter	0	5
Enterobacter	0	2
Serratia	0	1

Table 2 *Longitudinal study. prevalence of trimethoprim resistant organisms*

Case No	*Months from beginning of study*											
	0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
1	C	C	—	—	—	—	—	—	—	—	C	—
2	—	—	C	C	C	—	—	C	C			
3	—	—	—	—	—	—	—	—	—	—	—	—
4	C	—	—	C	S	C	C					
5	—	—	—	—	C	—	—					
6	—	—	—	C	—	C						
7	—	—	—	P	C	C						
8	—	—	—	—	—							
9	—	—	—									
10	—	—	—									
11	—	—										
12	—	—										
13	—	—										

C=*E coli*, S=*Serratia*, P=*Proteus*

Discussion

Sulphamethoxazole and trimethoprim inhibit two enzymes necessary for bacterial synthesis of folic acid. The combination, co-trimoxazole, was introduced in the hope that the chances of mutations in two genes would be low and thus the development of resistance slight. Indeed, in comparing long term treatment of recurrent urinary tract infections with co-trimoxazole or trimethoprim alone Pearson *et al* found a decreased incidence of recurrence from 41·4% to 6·3% with co-trimoxazole and only six infections were due to trimethoprim resistant bacteria [10] In another study patients given either co-trimoxazole or trimethoprim for four weeks were found to have a decreased number of faecal coliforms, but resistance to trimethoprim was encountered.[7] This occurred mainly in patients given trimethoprim alone. The rapid emergence of increased resistance to trimethoprim in the community was shown in a more recent study in which co-trimoxazole, trimethoprim, or placebo was given to a healthy group of students for only two weeks.[6] High levels of trimethoprim and sulphonamide resistance were encountered in the co-trimoxazole or trimethoprim groups. *E. coli* isolated was predominantly trimethoprim resistant.

Initial reports on the prophylactic use of co-trimoxazole in patients with leukaemia have shown a decrease in the number of infective episodes.[3–5]

Subsequent reports have indicated that such treatment selects for trimethoprim resistant coliforms[11] and patients could become infected with such bacteria.

In children with leukaemia co-trimoxazole is given prophylactically in an attempt to prevent *Ps. carinii* infections. During the study no child became infected. There is no doubt, however, that the use of co-trimoxazole in our patients selected for trimethoprim resistant bacteria. Sixty one per cent of those who received prophylaxis with co-trimoxazole were found to be excreting trimethoprim resistant bacteria, mainly *E. coli,* whereas only 14% of children who did not receive prophylaxis with co-trimoxazole were excreting such bacteria. Co-trimoxazole also apparently coselected for resistance to sulphonamides as 96% of the trimethoprim resistant bacteria isolated from the children with leukaemia were resistant compared with 82% of the control population. Most isolates from both groups were resistant to ampicillin and ticarcillin, but there was no evidence of resistance to gentamicin or tobramycin. The fact that 88% of the trimethoprim resistant bacteria were also resistant to streptomycin and spectinomycin may provide an insight into the genetics of this resistance as genes for resistance to trimethoprim, streptomycin, and spectinomycin are located on a single transposon (Tn7).[12]

No patient became infected with trimethoprim resistant bacteria during treatment with co-trimoxazole. It is noteworthy that trimethoprim resistant Gram positive bacteria were not selected by this prophylactic regimen as 70% of episodes of bacteraemia in our patients with leukaemia are due to Gram positive bacteria, such as *Staphylococcus aureus* and *Streptococcus pneumoniae* (unpublished data). In the longitudinal study 15% of patients were already colonised by trimethoprim resistant coliforms before treatment, which is in close agreement with the prevalence of resistance in the control population. Colonisation did not occur until the second month of prophylaxis and in most patients was intermittent.

As it is necessary to include prophylaxis for pneumocystis infection it is fortunate that although co-trimoxazole selects for resistant coliforms in the gastrointestinal tract, such bacteria, to date, have rarely caused serious infection It would also seem that co-trimoxazole has not yet selected for plasmids that encode resistance to many different antimicrobials and, in particular, to gentamicin or tobramycin. Regimens for treatment of acute lymphoblastic leukaemia, however, have become increasingly intensive, with a high incidence of profound neutropenia and increased side effects from chemotherapy. This, in particular, gives increased potential for invasive infections of gut origin and remains so throughout continuing treatment[13] Vigilance is therefore necessary with regard to the increased prevalence of trimethoprim resistant bacteria in the gastrointestinal tract of children with leukaemia and the potential for selecting resistance to many commonly used antimicrobials.

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Anorectal malformation: familial aspects and associated anomalies

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SUMMARY One hundred and sixty nine patients with anorectal malformation were stud were 108 boys, 60 girls, and one case of intersex. Low malformations were more comm sexes. Over half the subjects had associated malformations. These were more comm group with high malformations. There was no difference between the sexes in this r family history of similar malformation was found in 15 cases (9%). Where malformation was the only abnormality in the family an autosomal dominant mode of in was likely, except in one case where there was consanguinity. Where there were malformations no single mode of inheritance emerged. Two families with probabl unrecognised recessive syndromes are described. In most cases of anorectal malform recurrence risk is low. Multiple associated malformations may indicate recessive inheri subsequent pregnancies should be regarded as high risk and full antenatal investigativ provided.

Anorectal malformations (ARM) are common, occurring in about one in 5000 births.[1] There is wide variation in the type of malformation and the range of associated abnormalities.[2] There are many published reports of single family studies, and all forms of Mendelian inheritance have been described. Other authors have looked at the prevalence of associated abnormalities in subjects and their families and have described various syndromes and associations. Most of these reports are on small study samples and their value to the genetic counsellor is limited.

The object of this retrospective study was to ascertain all live births of infants with ARM during an eight year period in the north west of England. Notes were examined to discover what proportion had other malformations and which body systems were most commonly affected. Note was made of any family history of similar abnormality. The information was analysed to identify possible syndromal associations and patterns of inheritance that might allow more accurate estimation of recurrence risk

Patients and methods

Details of all infants with ARM admitted to the regional neonatal surgical centres between 1974 and 1981 inclusive were obtained from the hospital activity analysis, backed up by surgica The regional computer records were stud up early neonatal deaths and minor ab that had not been referred to the regior Unfortunately, because of the large hospitals involved and incomplete record possible to trace stillbirths with ARM. notes of every child were studied and t medical and family details extracted. sorted on the basis of sex and divided int low type of ARM as defined by Wilkin were also grouped according to whether was the only abnormality (isolated whether there were congenital abnorm affected other body systems (multiple g groups were compared using the χ^2 tes affected family members were mentione cal records of the relatives were obtai possible.

Results

A total of 169 cases was identified, o (17%) had died by the time of study. Tv deaths were unrelated to the congenital ity (One drowned at the age of 3 years and the other was a cot death at 3 mont cause found at postmortem examinatio

There were 108 boys (64%) and 60

plus one case of intersex (karyotype not known). The relative numbers of high and low malformations and their relation to sex is shown in Table 1.

In 80 cases (47%) the ARM was the only abnormality recorded. Of these, 48 (60%) were boys and 32 (40%) girls In 67 of these 80 cases (84%) the abnormality was of the low type and in 13 (16%) of the high type.

Five of the isolated group had a family history of ARM. In three of these the propositus was a boy and the father had an ARM. The fourth case with a positive family history was also a boy, with an affected half brother In the fifth case the propositus was a girl whose parents were consanguineous and whose first cousin also had an ARM. In all cases except the girl the ARM were of the low type

In 88 cases the ARM was associated with other abnormalities (multiple group). This group showed a more pronounced preponderance of boys (60 boys (68%) *v* 28 girls (32%)), although the difference in sex distribution between multiple and isolated groups was not significant ($p>0{\cdot}05$)

The proportion of high ARM was greater in the multiple group (58%, $p<0{\cdot}01$). Altogether, 80% of infants with a high ARM had other malformations compared with 36% of those with a low ARM. The distribution of the type of associated abnormalities for the group as a whole and for each sex is shown in Table 2.

Table 1 *No of high and low anorectal malformations in 169 patients according to sex*

	(n)	*No (%) of anorectal malformations*	
		High	*Low*
Boys	(108)	47 (44)	61 (56)
Girls	(60)	17 (28)	43 (72)
Total	(169)*	65*(38)	104 (62)

*One intersex case

Ten infants with multiple abnormalities had a family history of ARM. There was an equal number of high and low ARM and a boy:girl ratio of 7:3. Full details are shown in Table 3.

There were six cases of consanguinity, five of whom were boys and one girl In every case the parents were first or second cousins and were of Asian origin.

Several cases fitted the pattern of recognised syndromes or associations: Pfeiffer's syndrome, Frazer's syndrome, Downs' syndrome (three cases), C syndrome, fragile X syndrome, omphalocoele, extrophy of the bladder, imperforate anus, and spinal defect complex, and vertebral defects, imperforate anus, tracheo-oesophageal fistula, and radial and renal dysplasia association (eight cases). Note was made of any possible teratogens. A wide variety of drugs had been taken in the pregnancies but in only one case was there possible teratogenicity, this being in a mother who had taken Tridione throughout her pregnancy. One mother had been exposed to rubella in early pregnancy but congenital infection was not proved. Two mothers had diabetes.

Discussion

This study shows that low ARM are more common than high ARM and suggests that the incidence is greater in boys than in girls. This is in keeping with the findings of other workers.[4 5] When analysed this male predominance seemed to relate mainly to the group with high ARM, 73% of which were boys compared with 59% in the group with low ARM. This apparent male predominance in the group with high ARM did not quite reach significance ($p>0{\cdot}05$). It has been suggested that the greater incidence of high ARM in boys is due to the influence of the development of the mullerian system between the alimentary and urinary systems in girls.[4]

Table 2 *Distribution of associated abnormalities in 169 infants with high and low anorectal malformation Values are No (%)*

*System**	*All cases*		*Boys*		*Girls*	
	*High (n=65)**	*Low (n=104)*	*High (n=47)*	*Low (n=61)*	*High (n=17)*	*Low (n=43)*
Genitourinary tract	39 (60)	28 (37)	25 (53)	15 (25)	14 (82)	12 (28)
Skeletal	20 (31)	15 (14)	13 (28)	10 (16)	7 (41)	5 (12)
Cardiovascular	14 (22)	10 (10)	12 (26)	5 (8)	2 (12)	4 (9)
Facial	13 (20)	10 (10)	9 (19)	5 (8)	4 (24)	4 (9)
Gastrointestinal	22 (34)	0	16 (33)	0	6 (35)	0
Single umbilical artery	8 (12)	1 (1)	4 (9)	0	4 (24)	0
Neurological	2 (3)	3 (3)	2 (4)	2 (3)	0	1 (2)
Miscellaneous	5 (8)	7 (7)	3 (6)	6 (10)	1 (6)	1 (2)

*One intersex case

Over half our subjects had associated abnormalities (53%), but the incidence was greater in the group with high ARM (80%), suggesting a more complex pathogenesis of high ARM.

Although multisystem involvement is slightly more common in boys than in girls (56% v 47%), this could be accounted for by the greater proportion of high anomalies in boys—that is, given the presence of a high ARM, multiple abnormalities are as likely in a girl as in a boy. In both sexes the other body system most commonly affected was the genitourinary tract. This is probably due to the anatomical and temporal proximity of the embryological development of the lower bowel and genitourinary tract. The high incidence of skeletal, cardiovascular, and facial anomalies found is less easy to explain and implies an early and generalised insult with maximum effect on those systems that undergo most active transformation at the time. A possible insult was identified in only a few cases in one case a drug (Tridione) was responsible and in four cases (three Down's and one fragile X syndromes) a chromosomal abnormality was responsible. The range of associated abnormalities was similar for both sexes and for the groups with high ARM and the group with low ARM, the only difference being that other gastrointestinal tract anomalies were only found in the group with high ARM. This may be because of the differing embryological origins of high and low ARM.[4]

One of the main aims of this study was to consider the familial nature of anorectal anomalies. Five examples of familial incidence were seen in the group with ARM only. In four of these the pattern was suggestive of an autosomal dominant mode of inheritance (Table 3, cases 1–5) In all cases within

Table 3 *Congenital abnormalities recorded in families of children with anorectal malformations*

Case No	*Sex*	*Type ARM*	*Other abnormalities*	*Other family cases*	
				Affected member	*Abnormalities*
1	M	Low	—	Father	Imperforate anus
2	M	Low	—	Half brother (paternal)	Anal stenosis
3	M	Low	—	Father	Imperforate anus
4	M	Low	—	Father	Imperforate anus
5	F	High	—	Second cousin (?sex)	Imperforate anus
6	M	Low	Skeletal Radial aplasia abnormal toes CVS ASD, VSD TGV, third atrium GUT Dysplastic kidneys Misc Pulmonary hypoplasia	Sister Sibling	Single (right) lower limb, abnormal forearm, dysplastic kidneys, imperforate anus Anencephaly
7	M	Low	GUT Bilateral hydronephrosis	Siblings (?sex)	Conjoint twins
8	M	High	Skeletal Abnormal vertebrae, dysplastic foot CVS Single ventricle, ASD, single AV valve, pulmonary atresia GIT Asplenia	Sister	Anal stenosis polydactyly single ventricle asplenia
9	M	High	Skeletal Broad and duplicated phalanges Facial Midface hypoplasia, low set ears, proptosis cleft palate GIT Ileal atresia, caecal atresia	Father	Broad phalanges
10	M	High	GUT Hydroureter Facial Accessory auricle	Paternal uncle	Accessory auricle
11	F	High	GUT Cloaca	Mother	Septate vagina
12	F	Low	Skeletal Toe webbing, Facial Facial asymmetry CNS Mental retardation Misc Hirsutism	Brother Mother	Toe webbing mental retardation Mental retardation
13	M	Low	CVS VSD GUT Shawl scrotum Facial Small lower face, Misc Umbilical hernia	Father	Similar facial configuration
14	F	Low	GUT Bifid vagina, hydronephrosis	Cousin (F) Aunt	Intact hymen "Double uterus"
15	M	High	GUT Hypospadias, bifid glans Facial "Odd facies"	Sister	Similar facial configuration

CVS=Cardiovascular, ASD=Atrial septal defect, VSD=ventricular septal defect, TGV=transposition of the great vessels, AV=anterior-ventral, GUT=genitourinary tract, GIT=gastrointestinal tract, CNS=central nervous system, Misc=miscellaneous these families the abnormality was a minor one and detailed examination of other family members might have yielded further cases, as in the family reported by Reid and Turner.[6] Here 18 members over four generations had low ARM in association with minor thumb and ear anomalies. Such features, which may not have been recorded in the case notes of our study patients, could be of value as markers of autosomal dominant inheritance. Other reports of families with low ARM have suggested an autosomal recessive or sex linked recessive mode of inheritance.[6–12]

In our study familial cases associated with multiple abnormalities were heterogeneous (Table 3). In two cases there had been multiple abnormalities in siblings: case 6 had a low ARM with associated radial aplasia, major cardiac malformation, dysplastic kidneys, and pulmonary hypoplasia. A stillborn sibling with a low ARM also had an abnormal forearm, a single lower limb, and dysplastic kidneys. A further sibling had been anencephalic and another pregnancy resulted in an early miscarriage. Case 8 had a high ARM with vertebral abnormalities, a dysplastic foot, a major cardiac anomaly, and asplenia. A female sibling had a low ARM, polydactyly, a similar cardiac anomaly, and asplenia. In both families 6 and 8, where no chromosome abnormality was detected. the conditions probably represent hitherto undescribed recessive syndromes

In case 9 a high ARM was associated with broad and duplicated phalanges, a facial abnormality, and higher gut atresias. The child's father had similar malformations of the hands and feet but no apparent gut or facial anomaly. Case 10 had a high ARM with hydroureter and an accessory auricle. A paternal uncle also had an accessory auricle. In these two families autosomal dominant inheritance with reduced penetrance is a possibility.

Familial genitourinary abnormalities were seen in families 11 and 14. In the former the propositus had a cloaca and the mother an abnormal vagina. In case 14 the propositus had a low ARM with a bifid vagina and hydronephrosis and a female cousin and an aunt also had abnormalities of the genitalia.

We have described several inherited forms of ARM. Where the anomaly is associated with minor thumb and ear abnormalities, autosomal dominant inheritance may be implied[7] and other family members should be carefully examined. In some cases of severe multiple abnormalities—for example, families 6 and 8—risk of recurrence is obviously high, but we have been unable to identify any consistent pattern to suggest autosomal recessive inheritance that would aid the genetic counsellor. Moreover, a search of the published works has not revealed any comparable cases, suggesting that such 'syndromes' are either unique to the individual families or very rare. We suggest that in families where a single case with ARM and multiple malformations occurs referral to a genetic clinic may be appropriate to establish if a rare syndrome diagnosis can be made, to discuss possible recurrence risks with the parents, and to inform them of any prenatal diagnostic tests that are available for future pregnancies

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Plasma thyrocalcitonin and parathyroid hormone concentrations in early neonatal hypocalcaemia

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SUMMARY During the first week of life serum calcium, phosphorus, magnesium, immunoreactive thyrocalicitonin hormone, and parathyroid hormone concentrations were determined daily in 36 preterm and 29 small for gestational age, full term healthy infants. Preterm babies with early neonatal hypocalcaemia had significantly higher concentrations of serum thyrocalcitonin hormone in the first four days of life than normocalcaemic preterm babies. Parathyroid hormone concentrations were similar in hypocalcaemic and normocalcaemic infants. In contrast, in the full term group no significant differences were detected in thyrocalcitonin hormone and parathyroid hormone patterns between hypocalcaemic and normocalcaemic subjects. This suggests two different pathogeneses for early hypocalcaemia in low birthweight infants. Hyperthyrocalcitoninaemia seems to be the main determining factor in preterm infants, while a non-hormonal pathogenesis should be considered in full term infants who are small for gestational age.

Hypocalcaemia occurs often in the neonatal period, mainly in preterm and small for gestational age, full term babies.[1–3] Late hypocalcaemia, which occurs after the third day of life, is associated with high phosphorus:calcium ratios in formula feeds and, more rarely, with hypomagnesaemia or hormonal disorders.[2 4–6] The pathogenesis of early hypocalcaemia, which occurs during the first 72 hours of life, has not been clearly defined,[7 8] although inadequate secretion of parathyroid hormone[8–11] and increased concentrations of thyrocalcitonin hormone[9 12 13] have been implicated. Until now, however, the different secretions of these hormones in the neonatal period has merely been related to the mean total serum calcium concentrations, without subdividing the studied population into those with and without hypocalcaemia.

The aim of the present study was to investigate the role of thyrocalcitonin and parathyroid hormones in the pathogenesis of early neonatal hypocalcaemia in hypocalcaemic and normocalcaemic babies who were either preterm or small for gestational age and full term.

Patients and methods

The study was carried out on 65 healthy low birthweight newborn babies (birth weight <2500 g) who were preterm (n=36) or full term (n=29). It was approved by the ethical committee of our department and had the informed consent of the parents. Gestational age was assessed according to the last normal menstrual period and confirmed by the Dubowitz scoring system.[14] Infants who were small for gestational age were defined according to the standards of Lubchenco *et al.*[15] All babies were nursed in incubators at normal temperature and fed the same standard formula within the first hour of life. Energy and fluid intakes per kg and per day were similar for all subjects throughout the study. No drugs or vitamin supplements were given during the study. Phototherapy was started when serum total bilirubin concentrations reached 205 µmol/l. Serum calcium, phosphorus, magnesium, thyrocalcitonin hormone, and parathyroid hormone concentrations, acid base state, packed cell volume, and haemoglobin, total bilirubin, glucose, and proteins concentrations were determined daily on capillary or central blood samples during the first week of life. Serum total calcium was determined by Eppendorf flame spectrophotometry,[16] and inorganic phosphorus[17] and magnesium[18] by a colorimetric method. Serum thyrocalcitonin and parathyroid hormones were determined by radioimmunoassay

(RIA): the RIA-mat Calcitonin II method measures thyrocalcitonin hormone values between 10 and 1000 pg/ml and the RIA-mat PTH method measures directly serum parathyroid hormone 1–84 equivalents from 15 to 1000 pmol/l in human serum (Byk-Mallinckrodt).

Hypocalcaemia was defined as a total serum calcium concentration less than 1·75 mmol/l in the first 72 hours of life. We compared serum calcium and thyrocalcitonin and parathyroid hormone concentrations firstly in preterm babies with small for gestational age full term babies and secondly in all babies who were hypocalcaemic with those who were normocalcaemic. All results are expressed as mean (SD).

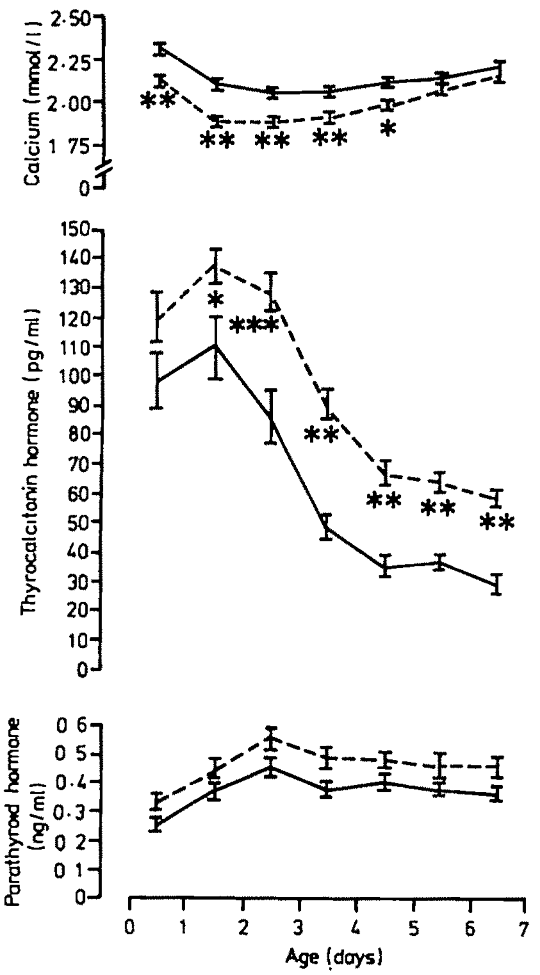

Fig 1 *Serum calcium, parathyroid hormone, and thyrocalcitonin hormone concentrations in preterm (——) and small for gestational age, full term (– – –) babies during the first week of life*

*p<0 05, **p<0 01, ***p<0·001

Statistical analysis was performed by the two tailed Student's *t* test and the correlation coefficient

Results

Preterm babies *v* small for gestational age, full term babies. The mean serum calcium and thyrocalcitonin and parathyroid hormone concentrations in preterm and small for gestational age, full term babies during the first week of life are shown in Figure 1 and clinical data on these study groups in Table 1. Mean serum calcium concentrations were significantly lower and mean serum thyrocalcitonin hormone concentrations significantly higher in preterm babies compared with small for gestational age, full term babies. No significant differences were detected in parathyroid hormone concentrations between the two groups

An inverse correlation was found in both the preterm and the full term babies between serum thyrocalcitonin hormone and calcium and between serum parathyroid hormone and calcium in the first three days of life. The correlation coefficient for thyrocalcitonin hormone and calcium concentrations was r=0·993 on day 1, r=0·995 on day 2, and r=0·983 on day 3 (p<0·01) and for parathyroid hormone and calcium concentrations was r=0·828 on day 1, r=0·839 on day 2, and r=0·847 on day 3 (p<0·02).

Hypocalcaemic *v* normocalcaemic babies.

Preterm babies

The incidence of early hypocalcaemia was 33·3% (12 of 36) in the preterm babies and 17·1% (five of 29) in the full term babies Mean concentrations of serum calcium and thyrocalcitonin and parathyroid hormones in hypocalcaemic and normocalcaemic preterm babies during the first week of life are shown in Figure 2 and clinical data on these study groups in Table 2. Serum calcium decreased after

Table 1 *Clinical data of the study groups Values are No or mean (SD)*

	Study group *Preterm infants*	*Small for gestational age full term infants*
(n)	(36)	(29)
Sex (M F)	14 22	12 17
Birth weight (g)	2033 (390)	2250 (184)
Gestational age (wks)	34 1 (1 6)	38 1 (1 1)

the first day of life in both groups, more markedly so in the hypocalcaemic group The lowest postnatal value in the hypocalcaemic group was 1·7 mmol/l on the second and third days of life and in the normocalcaemic group was 2·0 mmol/l on the third day of life Significant differences in calcium concentrations were observed between the two groups on the second, third, and fourth days of life ($p<0{\cdot}001$, $p<0{\cdot}001$, and $p<0{\cdot}01$, respectively). Mean thyrocalcitonin hormone concentrations were similar on the first day of life in the two groups. A pronounced increase in the mean serum thyrocalcitonin hormone concentration from 118 pg/ml to 169 pg/ml on the third day, was observed in the hypocalcaemic babies. Thyrocalcitonin hormone values in hypocalcaemic babies were significantly higher than in normocalcaemic infants on the second, third, and fourth days of life ($p<0{\cdot}01$, $p<0{\cdot}001$, and $p<0{\cdot}001$, respectively). Thereafter, similar thyrocalcitonin hormone concentrations were observed in both preterm groups. In both groups an increase in serum parathyroid hormone concentrations, more evident in hypocalcaemic (+113%) than in normocalcaemic (+62·8%) babies, was observed at between one and three days of life, followed by constant concentrations up to the seventh day. No significant differences in parathyroid hormone values and patterns between hypocalcaemic and normocalcaemic preterm infants were observed. Serum phosphorus, magnesium, total protein, and electrolyte concentrations, packed cell volume, and acid base state were similar in both preterm groups. No infant had a serum glucose concentration lower than 2·22 mmol/l and only 25 babies (12 of whom were hypocalcaemic and 13 of whom were normocalcaemic) were treated with phototherapy.

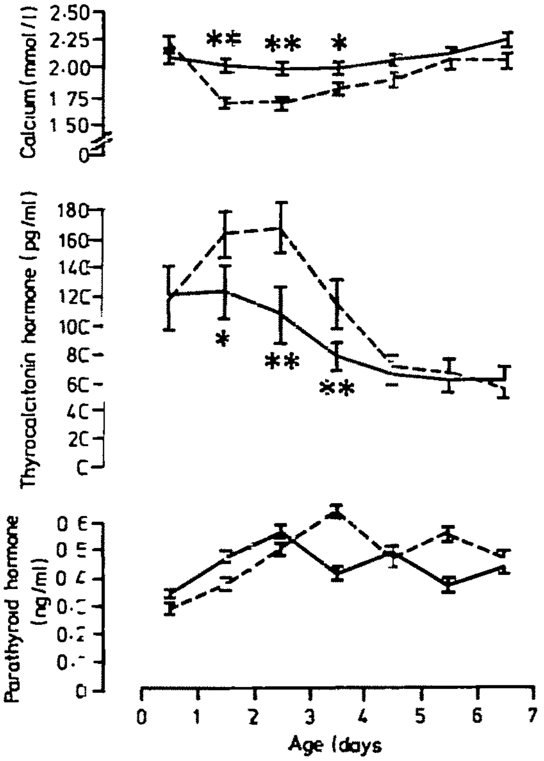

Fig. 2 *Serum calcium, parathyroid hormone, and thyrocalcitonin hormone concentrations in hypocalcaemic (– – –) and normocalcaemic (——) preterm babies during the first week of life.*

*$p<0{\cdot}01$, **$p<0{\cdot}001$

Table 2 · *Clinical data of hypocalcaemic and normocalcaemic patients within the preterm and small for gestational age, full term study groups. Values are No or mean (SD)*

	Hypocalcaemic patients	*Normocalcaemic patients*
Preterm babies		
(n)	(12)	(24)
Sex (M F)	6 6	8 16
Birth weight (g)	2 50 (310)	1975 (430)
Gestational age (wks)	34 1 (1 5)	34 1 (1 7)
Full term babies		
(n)	(5)	(24)
Sex (M F)	3 2	9 15
Birth weight (g)	2237 (204)	2260 (180)
Gestational age (wks)	37 9 (1 0)	38 2 (1 2)

Small for gestational age, full term babies
Figure 3 shows the mean serum calcium and thyrocalcitonin and parathyroid hormone concentrations for the hypocalcaemic and normocalcaemic small for gestational age, full term babies. The serum calcium concentration decreased in the hypocalcaemic group from the initial mean value of 2·2 mmol/l to 1·72 mmol/l on the third day of life; the lowest mean serum calcium concentration in the normocalcaemic group was 2·12 mmol/l on the fourth day of life. Thyrocalcitonin hormone concentrations showed a small increase in the first 24 hours and then decreased in both groups. A similar increase of serum parathyroid hormone values was observed in hypocalcaemic (+56%) and normocalcaemic (+74%) babies between one and three days. No particular trends of parathyroid hormone were then observed in either group Although significant differences in mean serum calcium concentrations were observed between the two groups on the second, third, and fourth days of life ($p<0{\cdot}01$, $p<0{\cdot}001$, and $p<0{\cdot}01$, respectively), no significant differences were detected in mean serum thyrocalcitonin and parathyroid hormone concentrations

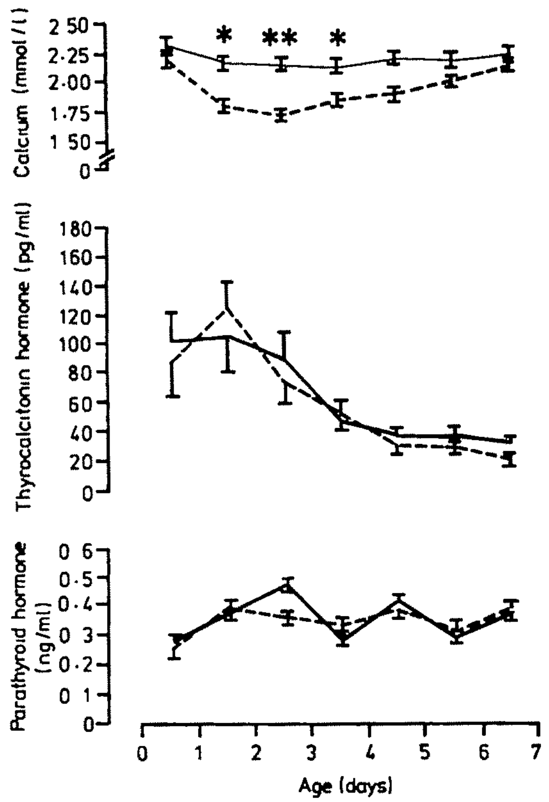

Fig 3 *Serum calcium, parathyroid hormone, and thyrocalcitonin hormone concentrations in hypocalcaemic (– – –) and normocalcaemic (——) small for gestational age, full term babies during the first week of life*

*$p<0\ 01$, **$p<0\ 001$

during the study. Serum phosphorus, magnesium, total protein, and electrolyte concentrations, packed cell volume, and acid base state were similar in hypocalcaemic and normocalcaemic small for gestational age, full term infants No full term infant had a serum glucose concentration lower than 2·22 mmol/l and 11 babies (five of whom were hypocalcaemic and six of whom were normocalcaemic) were treated with phototherapy.

No hypocalcaemic preterm or small for gestational age, full term infants had any important clinical symptoms All those with hypocalcaemia recovered spontaneously, except for two (one preterm baby and one full term baby), whose early hypocalcaemia was followed by late hypocalcaemia, which was treated orally with vitamin D and 10% calcium gluconate solution.

Discussion

Our results indicate that the increase in thyrocalcitonin hormone concentrations observed in preterm and small for gestational, full term babies in the first 24 hours of life is associated with a fall in serum calcium concentrations, in spite of rising parathyroid hormone concentrations. Preterm babies had significantly higher thyrocalcitonin hormone concentrations and significantly lower calcium concentrations compared with the small for gestational age, full term infants during the whole of the first week of life. Moreover, our study confirmed the higher incidence of early hypocalcaemia in the preterm compared with the full term babies, as previously reported.[5 8]

One possible cause of early hypocalcaemia is a transient state of neonatal hypoparathyroidism, secondary to fetal hypercalcaemia.[8 9] Yet in our study no significant differences in parathyroid hormone values were observed between hypocalcaemic and normocalcaemic preterm and small for gestational age, full term infants. On the contrary, our finding of a rapid postnatal increase in parathyroid hormone strongly suggests, as previously reported,[12] an effective response of parathyroid glands to falling serum calcium concentrations, gestational age not being a conditioning factor for this response.

The physiological role of thyrocalcitonin hormone in the regulation of neonatal calcium metabolism remains to be clarified. High thyrocalcitonin hormone concentrations in cord blood,[12] as well as a rise in the concentrations of this hormone during the first hours of life,[10 13] possibly influence the fall in serum calcium concentrations during the neonatal period. The significant differences we found in serum thyrocalcitonin hormone concentrations between hypocalcaemic and normocalcaemic preterm babies during the first three days of life support this hypothesis. In contrast, the observation that hypocalcaemic and normocalcaemic small for gestational age, full term infants showed similar trends in thyrocalcitonin hormone concentrations during the study suggests a non-hormonal pathogenesis of the early hypocalcaemia in these babies. The interruption of the transplacental calcium transfer is probably more important in this group of babies.

As it has been shown that defective vitamin D metabolism is not a primary factor in the pathogenesis of early neonatal hypocalcaemia,[11] and also that vitamin D supplementation fails to prevent early neonatal hypocalcaemia in premature infants,[20] vitamin D and its active metabolites were not measured in this study.

Our study suggests a different pathogenesis for early hypocalcaemia in preterm babies and small for gestational age, full term babies. A higher and longer secretion of thyrocalcitonin hormone is the main determining factor of early hypocalcaemia in preterm babies, while a non-hormonal cause should be considered for early hypocalcaemia in small for gestational age, full term infants. It is not clear why only some preterm babies have hyperthyrocalcitoninaemia during the early neonatal period. A relation between mode of delivery and thyrocalcitonin hormone concentrations during the first hours of life has been reported (Bagnoli F, De Leo V, Bruchi S, Buonocore G, Berni S, Tallini B, Bracci R. Calcitonin, parathyroid hormone and prolactin concentrations in the first days of life in relation to the mode of delivery, presented at the International symposium on the endocrine physiology of pregnancy and peripartum period Siena, April 1984). Our data did not show this relation in either premature or full term infants.

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Parvovirus associated aplastic crisis in homozygous sickle cell disease

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SUMMARY Aplastic crises in homozygous sickle cell disease in Jamaica predominantly affect children and occur in epidemics. Of 67 cases in a cohort study of 314 children with homozygous sickle cell disease, 62 were attributable to human parvovirus infection. Affected children were aged 0·5–12·5 years, and the incidence rose to 28% by 10 years. No recurrences were seen. Symptoms and signs on presentation were attributable to the viraemia and acute anaemia. Asymptomatic thrombocytopenia was common. Blood transfusion was given in 54 cases (87%). Thirty eight children (61%) were admitted to hospital, 16 of whom were extremely ill on presentation and one of whom died soon after admission. Twenty four (39%) were managed as outpatients, 16 of whom were transfused. Parvovirus associated aplastic crisis is a self limited condition with excellent prognosis if diagnosed promptly and managed appropriately.

The aplastic crisis occurs in a variety of chronic haemolytic conditions.[1–4] A temporary stopping of erythropoiesis is followed by a rapid fall in haemoglobin concentration, and death may result from peripheral circulatory failure Most episodes are associated with human parvovirus infection.[3 5–8] Of 67 aplastic crises in a cohort study of sickle cell disease, 62 were attributable to parvovirus infection.

Patients and methods

Three hundred and fourteen children with homozygous sickle cell disease were identified during the screening of 100 000 consecutive babies at the main Government Maternity Hospital (Victoria Jubilee Hospital) between 1973 and 1981. These children are being prospectively followed up in a cohort study and the methods of diagnosis,[9] follow up, and haematological investigations[10] have been described previously

The aplastic crisis was defined as a fall in haemoglobin markedly below steady state values associated with absence of or very few ($\leqslant$1%) reticulocytes in the peripheral blood. With higher concentrations of reticulocytes, the diagnosis was only accepted if there was a daily increase consistent with the recovery phase of the aplastic crisis. These haematological criteria were met in 67 children, of whom 62 had evidence of concurrent parvovirus infection. The diagnosis of recent parvovirus infection was based on the finding of viral deoxyribonucleic acid (DNA) in acute serum samples (16 cases), parvovirus specific IgM in acute or convalescent serum samples (27), or seroconversion (19).

Fifty four children presented to special cohort clinics and eight to the casualty department.

Results

Three epidemics of aplastic crisis occurred during the study—namely, in 1973–75, 1979–80, and 1984–86. No aplastic crises were seen between these epidemics. One, 24, and 37 cohort children were affected in the three epidemics, respectively, representing an overall prevalence of 20% and an incidence of 28% by 10 years. The youngest child was 0·5 years and four were affected in the first year. Sexes were affected equally (35 boys and 27 girls).

Clinical features. A prodromal illness was reported in 61 children, one episode being diagnosed retrospectively during a routine blood test. The prodrome averaged two to three days (range one to 14 days), and the prodromal symptoms are listed in Table 1.

The major signs on examination are summarised in Table 2 The oral temperature, measured in 54 children, was 37·1–38°C in 19 (35%) and exceeded 38°C in 23 (43%). Splenomegaly increased in size in

Table 1 *Prodromal symptoms in 62 aplastic crises*

Symptoms	*No (%) with that symptom*
Fever	2 (68)
Headache	2 (35)
Abdominal pain	0 (32)
Upper respiratory infection	8 (29)
Anorexia	4 (23)
Limb pain	3 (21)
Vomiting	9 (15)
Pallor	9 (15)
Weakness	8 (13)
Breathlessness	3 (5)

Table 2 *Major signs on examination in 62 aplastic crises*

Sign	*No (%) with that sign*
Pallor	54 (87)
Tachycardia	23 (37)
Hepatomegaly (3 cm)	13 (21)
Gallop rhythm	10 (16)
Pharyngitis	9 (15)
Otitis media	6 (10)
Chest signs	4 (6)
Confusion	4 (6)
Neck stiffness	3 (5)
Dehydration	3 (5)

four children (aged 0·6–3·6 years), all of whom had evidence of heart failure. A macular rash on face and trunk occurred one week before aplasia in a child aged 7·5 years, and another aged 6 years had generalised pruritis but without a rash at presentation.

Familial involvement was common, aplastic crises developing in six of nine siblings with homozygous sickle cell disease of affected children at intervals of seven to 32 days after the index case.

A girl aged 5·5 years had the simultaneous occurrence of parvovirus infection and salmonella septicaemia. She was ill and drowsy at presentation with only a slight pallor, and her platelet count was 100 000 above steady state. Her haemoglobin concentration had fallen from 9·1 to 6·2 g/dl and reticulocyte count from 3% to 0·8%. A blood sample grew *Salmonella St Paul* but also manifested 60 arbitrary units of parvovirus specific IgM, confirming recent parvovirus infection.

Haematological investigations. Mean haemoglobin concentration at presentation was 3·9 g/dl (range 1·8–8·5 g/dl), representing an average fall of 3·9 g/dl (range 1·7–6·9 g/dl), below the individual's steady state values. Reticulocytes were absent from the peripheral blood in 43 cases (69%), between 0·1 and 1·0% in 14 (23%), and between 6 and 25% in five, all of whom seemed to be in the recovery phase of the aplastic crisis. The return of reticulocytes—that is, recovery—was monitored in 38 of 57 patients who presented in the acute phase of the aplasia and occurred in one to three days in 11 children, four to six days in 11, and seven to 10 days in 16.

Mean cell volume at the time of aplasia was available in 60 of the 62 patients and was within 5 fl of steady state values in 39 (65%), fell in 12, and rose in seven. Total serum bilirubin concentrations at the time of aplasia were available in 24 of the 62 patients and were unchanged (±5 μmol/l) in five. In one patient the total bilirubin concentration increased from 34 to 48 μmol/l, but 18 showed an average fall of 19 μmol/l (range 5–72 μmol/l).

Total white blood cell counts (total nucleated cell counts corrected for nucleated red cells) were available in 46 of the 62 patients and were within 2000 of previous steady state values in 10. Counts fell in 22 patients, of whom 19 showed decreases of 3000–9000 and three decreases of 12 000–17 000. Counts increased in 14 patients, of whom four had increases of 5000–9000 and 10 increases of 11 000–45 000.

Platelet counts at the time of aplasia were measured in 37 children and were within 25 000 of steady state in four. They fell in 27 children (73%) by a mean of 201 000 (range 62 000–584 000) below steady state values and were below 150 000 in four, although none had spontaneous bleeding. They increased in six children, two of whom were in the recovery phase of aplasia, one of whom had a concomitant salmonella septicaemia, and three of whom had no explanation.

Fetal haemoglobin concentrations at the time of aplasia were measured in 25 children and did not deviate by more than 5% of previous steady state values in three patients. In 22 children fetal haemoglobin concentrations showed a mean proportional increase of 58% (range 10–133%).

Serum iron concentrations at the time of aplasia were available in 20 children and were unchanged in two. The concentrations increased in 16, often strikingly, the concentrations exceeding 36 μmol/l in seven and iron saturations exceeding 70% in eight. These concentrations generally fell precipitately with the recovery of erythropoiesis.

Management. A single transfusion of packed red cells was given in 54 children (87%). Of the eight children not receiving transfusion, three were in the recovery phase, one refused on religious grounds, and four had only modest decreases in haemoglobin concentrations.

Blood cultures, performed in 48 cases (77%), yielded one pathogen, a *Salmonella St Paul* spp.

Cerebrospinal fluid was sterile in all six cases examined Antibiotics were prescribed for possible bacterial infection in 44 children (71%) (seven cases of clinical pneumonia, five of tonsillitis or pharyngitis, four of otitis media, one of burns, and 27 of unexplained fever).

In the first two epidemics 22 of 25 patients (88%) were admitted to hospital, but in the last epidemic only 16 of 37 (43%) were admitted Of these, eight presented late in the day or out of clinic hours and eight had complications (two had acute circulatory collapse, two had possible septicaemia, and one each had dehydration, painful crisis, pneumonia, and transfusion reaction). Only these eight (22%) required admission for medical reasons. The changing attitude to admission to hospital reflected increased familiarity with the natural history, good prognosis with appropriate management, and increased use of outpatient transfusion and close follow up.

Outcome. One child died from circulatory collapse because an incorrect diagnosis in the casualty department led to a six hour delay in transfusion. The remaining 61 patients recovered uneventfully and none manifested recurrences

Discussion

Chronic haemolytic anaemias are generally associated with expansion of bone marrow and a compensatory increase in erythropoetic activity. In the aplastic crisis there is a sudden and self limited stopping of marrow activity that predominantly affects erythroid maturation, which results in an absence, or very few immature red cells (normoblasts or reticulocytes) in the peripheral blood In chronic haemolytic processes, because of the short survival of red cells, these events are rapidly reflected in the peripheral blood and manifest by a rapid fall in haemoglobin concentration. Such aplastic crises have been recognised in a variety of chronic haemolytic anaemias.[1–4]

It is vital to distinguish aplastic crises from hypoplastic episodes, which may attend certain infections (salmonella, pneumococcus, and mycoplasma), metabolic disturbances (renal failure), or nutritional abnormalities (folate deficiency). All may be associated with a lower reticulocyte count (1–5%) and haemoglobin concentration (usually 4–6 g/dl) compared with steady state values. When clearly defined (as proposed in this paper) the aplastic crisis emerges as a separate entity that, in most episodes, is associated with human parvovirus infection.

In Jamaica aplastic crises follow a clear epidemic pattern with a four year interval between peaks, individual epidemics usually lasting 18–24 months. Human parvovirus infection accounted for 62 of 67 (93%) episodes, and although no cause was found for the other five episodes, it is of interest that they occurred during the parvovirus related epidemics. Other causes of aplasia are reported[11] and occasional combined infections may occur.[12] Children with homozygous sickle cell disease do not seem to be more prone to parvovirus infection and this infection does not always result in clinically recognised aplasia.[6] Clarification of the temporal relation between parvovirus infection and aplastic crises must await sero-epidemiological studies already underway.

The mechanisms of parvovirus induced aplasia have been discussed elsewhere.[13 14] Experimental human parvovirus infection of normal volunteers resulted in disappearance of reticulocytes, a fall in white blood cell and platelet counts, but only a slight fall in haemoglobin concentration.[15] These features are all apparent in parvovirus related aplasia in homozygous sickle cell disease, although the haemoglobin fall is more pronounced because of the short survival of red cells. There is also a fall in bilirubin, a rise in serum iron, and a striking increase in fetal haemoglobin because of the greater survival of cells containing high amounts of fetal haemoglobin. These findings are diagnostic of the aplastic crisis and bone marrow examination is rarely necessary.

The clinical features are consequent on these haematological changes and the profound anaemia requires urgent blood transfusion. Other complications may necessitate admission to hospital, but in uncomplicated cases the predictable natural history and uniformly good prognosis generally allow outpatient management Bone marrow activity returns spontaneously usually after a period of eight to 10 days and a pronounced reticulocytosis is associated with a rapid return to steady state haemoglobin concentrations.[16] Patients should continue to be monitored during this period as a slower response may indicate superimposed iron or folate deficiency. Siblings with homozygous sickle cell disease should be watched for aplasia, because of the familial tendency and cross infection that may occur in the hospital ward.[17]

Skin changes are of particular interest because human parvovirus seems to be responsible for the maculopapular rash of erythema infectiosum,[18] and a similar rash occurred in inoculated human volunteers. They are rarely recorded in human parvovirus related aplasia in sickle cell disease, although they did occur in one case in the present study. The reasons for this different behaviour are unknown.

Aplastic crises rarely, if ever, recur. Recurrent parvovirus related aplasias have never been reported and life long immunity seems to follow infection. A human parvovirus vaccine currently under development may therefore be effective in preventing this complication.

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Computed tomography in severe protein energy malnutrition

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SUMMARY Computed tomography of the brain was performed on eight children aged 1 to 4 years with severe protein energy malnutrition. Clinical features typical of kwashiorkor were present in all the children studied.

Severe cerebral atrophy or brain shrinkage according to standard radiological criteria was present in every case. The findings of this study suggest considerable cerebral insult associated with severe protein energy malnutrition.

The possible long term effect of protein energy malnutrition on the developing brain remains a controversial issue. Stoch and Smythe, in a now famous series of articles, showed retardation of intellect and reduced head circumference that indicated impaired brain growth in long term follow up of individuals who had been severely undernourished during infancy [1-4] Moodie *et al* in a 15 year follow up of patients with kwashiorkor in Cape Town, South Africa, found that both patients and controls had lower than average scholastic achievement and problems with social adjustment.[5] Their findings suggested that other environmental factors have greater effect. Dobbing, in a recent review of infant nutrition and its effect on later achievement, concluded that brain growth is indissolubly linked with body growth.[6] Promotion of somatic growth in the period before the second and even third birthday is important in his opinion to ensure good brain growth.

Severe cerebral atrophy was found initially on a computed tomogram of a child with kwashiorkor admitted to the paediatric wards of the Pelonomi Hospital in Bloemfontein. A review of the published works revealed that this finding had not been reported previously, although an echoencephalographic study had shown dilated ventricles in infants with kwashiorkor but not in infants with marasmus.[7] Subsequent to this initial observation, a further seven children admitted with severe malnutrition and clinical signs of kwashiorkor or marasmic kwashiorkor were examined by computed tomography of the brain.

Patients and methods

Eight children aged 1 to 4 years (median 17·5 months) were studied. All but one were boys and all were admitted primarily for management of severe protein energy malnutrition.

All were growth retarded, with growth variables less than the third centile of the National Center for Health Statistics[8] (Table). In four the body mass was less than 60% of expected weight for age, indicating severe malnutrition or marasmic kwashiorkor. Head circumference was measured in five and was normal for age in four. In the other child the head circumference was appropriate for mass and height, both of which were far below the normal for age. In

Table *Nutritional and growth variables in the eight cases admitted primarily for management of severe protein energy malnutrition*

Case No	*Variable*		
	Mass (NCHS centile)	*Head circumference (NCHS centile)*	*Albumin (g/l)*
1	<3	N	15
2	<60% EW	<3	18
3	<3	N	14
4	<3	—	18
5	<60% EW	N	10
6	<60% EW	—	23
7	<3	N	18
8	<60% EW	—	18

NCHS=National Center for Health Statistics.[8] EW=expected weight for age
N=normal

three patients the head circumference was not recorded but head size was regarded as appropriate for body size on clinical examination. Serum albumin concentrations were extremely low in all eight patients and in seven were below 20 g/l.

All had clinical features of kwashiorkor, such as generalised oedema, skin lesions, and hair changes. All were typically apathetic and withdrawn on admission. One child had generalised convulsions intermittently over a period of five days after admission, despite treatment with anticonvulsants. Examination of cerebrospinal fluid and serum biochemistry showed no abnormality, and no definite cause for the convulsions was found. Another child had shortlived convulsions on admission when critically ill with pneumonia and presumed septicaemia. At this time he had an uncompensated metabolic acidosis (pH 7 17) and hyponatraemia (sodium concentration 108 mmol/l). Hyponatraemia was presumed to be the cause of the convulsion.

Most (six of the eight) had diarrhoea on admission, but this responded to standard treatment and had resolved at the time of computed tomography. One patient, aged 4 years, was admitted initially for kwashiorkor, but further investigation revealed polyposis coli with juvenile polyps that affected the entire colon. He had a severe protein losing enteropathy, which resulted in his malnourished state.

At the time of computed tomography all were stable clinically, were normally hydrated, and had normal acid base and electrolyte values. Most were scanned one to two weeks after admission. The tomograms of the brain were performed according to standard procedure without sedation or contrast. Consent for computed tomography was obtained from the parents in each case.

Results

The findings on computed tomography were identical in all eight children. There was pronounced enlargement of the ventricles and cerebral sulci (Figures 1, 2, and 3), indicating a severe degree of cerebral atrophy or 'brain shrinkage'. The cerebellum was relatively spared (Fig. 4) and did not show the severe degree of volume loss seen in the cerebral hemispheres. No other abnormalities were evident on computed tomography.

All children were discharged after periods of admission to hospital of between four and six weeks, without gross neurological deficit, apart from the child with prolonged convulsions, who had residual spasticity. The child with juvenile polyposis was readmitted one month later, at which time a total colectomy was performed. The protein losing enteropathy resolved postoperatively with improvement in the nutritional state. Long term follow up of these patients is not available.

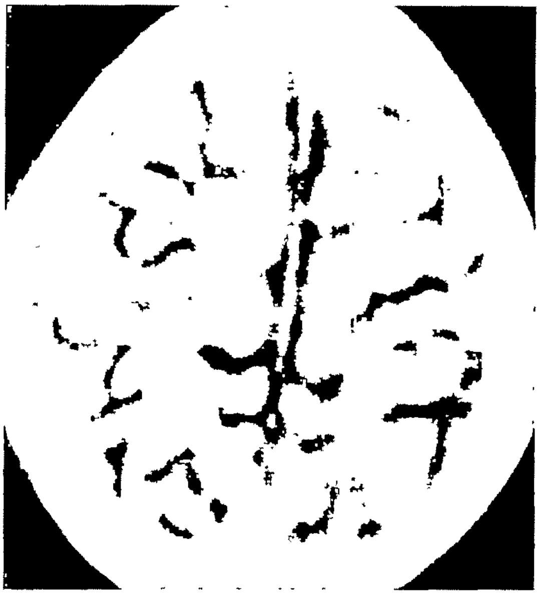

Fig 1 *Computed tomogram of case 3, showing wide cerebral sulci*

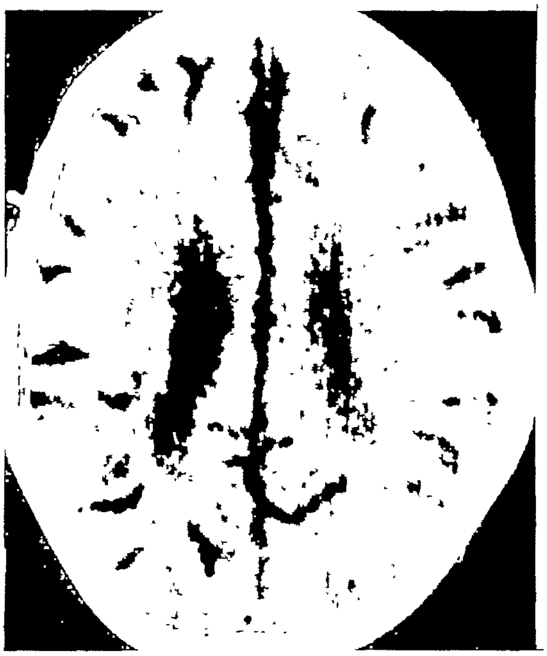

Fig 2 *Computed tomogram of case 5, showing widened cerebral sulci and enlarged ventricles*

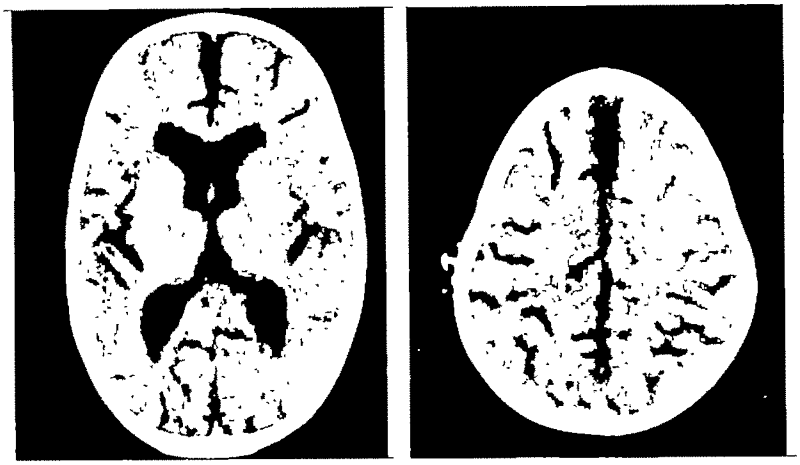

Fig 3 *Computed tomograms of case 6, showing diffuse cerebral atrophy or shrinkage*

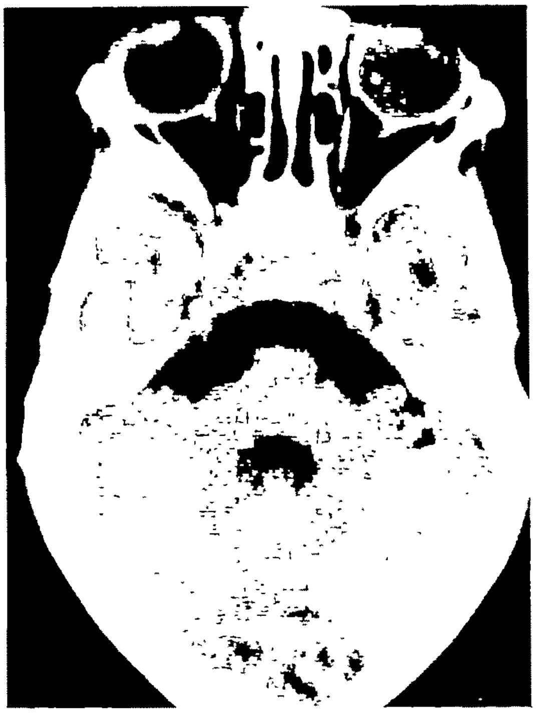

Fig 4 *Computed tomogram of case 6, showing relative sparing of the cerebellum*

Discussion

The findings of this small study indicate a loss of brain volume associated with severe protein energy malnutrition in young children. The loss of brain volume is almost certainly the result of cerebral atrophy rather than a temporary reduction in brain interstitial fluid volume. The latter could produce a similar though less severe picture. The fact that these patients were well hydrated with normal serum electrolyte concentrations and had a lowered serum colloid osmotic pressure due to hypoalbuminaemia at the time of computed tomography makes this unlikely in our opinion. It is accepted that cerebral atrophy could have resulted from metabolic, haemodynamic, or infective causes in these ill children The fact that all had severe cerebral atrophy without evidence of any other abnormality, however, strongly suggests an association with the present of severe protein energy malnutrition, which was the common factor in all eight children

Computed tomography allows the easy demonstration of ventricular size and the appearance of the cerebral sulci.[9] Before the development of computed tomography the only reliable method of showing cerebral atrophy was pneumoencephalography. It must be emphasised that cerebral atrophy shown by computed tomography is a strictly morphological observation. There is not necessarily a direct correlation with the functional capacity of the brain.[9]

Studies have shown that intellectual functions may be well preserved in patients with radiologically or pathologically shown cerebral atrophy, while profoundly demented patients may have morphologically normal brains.[9] Cerebral atrophy or loss of brain substance has been shown with advancing age in otherwise normal individuals.[10] On the other hand, cerebral atrophy may be associated with pathological conditions such as neurodegenerative disorders—that is, mucopolysaccharidoses, mucolipidoses, and the leucodystrophies—in childhood[11] Cerebral atrophy, or brain shrinkage, has been found to be associated with severe nutritional deficiency states in adults, such as anorexia nervosa and Wernicke's encephalopathy with alcohol abuse.[12] In these states there is selective reduction of white matter and reduced brain weight at postmortem examination.

What then is the importance of the brain shrinkage found in all eight children studied? It has been shown that the human brain undergoes a growth spurt from the mid-trimester of gestation until 2 or 3 years of age.[13] Neuronal numbers reach their full complement between the 10th and 20th weeks of gestation Increase in brain substance thereafter is the result of massive glial multiplication and the process of myelination[13] Of considerable functional importance is the development of synaptic connections and the growth of dendritic tree at this time. The considerable loss of brain substance and, by inference, myelin during this critical period shown in the malnourished children studied may indicate permanent damage to their developing brains. Animal experiments have shown that failure of synaptogenesis and reduction in the degree of dendritic complexity produced by undernutrition at this time is probably irreversible.[14] Follow up studies of these children would be of interest to assess if the cerebral atrophy is a persistent finding. Such a long term study is currently being undertaken and we hope to report the findings in due course.

Of particular interest is the report that five of the 20 infants with severe malnutrition in infancy studied by Stoch and Smythe had abnormal computed tomograms at 20 to 24 years of age.[15] The subtle signs of underdevelopment in the temperoparietal region on computed tomography correlated positively with tests for disturbance of visuomotor organisation when compared with the remaining 15 individuals in whom computed tomograms were normal

In conclusion, the findings of this small series further support the view that severe protein energy malnutrition in early childhood is a factor likely to result in reduced intellectual potential. Many environmental factors, including nutrition together with inherent genetic potential, play an important part in determining the final outcome of the developmental process. The relative importance of nutrition with regard to the ultimate achievement of the individual in later life remains to be determined.

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How should chylothorax be managed?

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SUMMARY The management and complications of chylothorax occurring beyond the neonatal period were reviewed retrospectively. Records from 15 patients treated between 1976 and 1986 were analysed; a combination of thoracocentesis, chest drain insertion, and dietary modification were successful in abolishing chyle leakage in 10 cases. One child died from complications of cardiac surgery rather than from the chylothorax, and surgical intervention was necessary in the remaining four patients and included pleurectomy in three and thoracic duct ligation in the fourth. Lymphopenia, hypoalbuminaemia, hyponatraemia, and weight loss were the most common complications of conservative management and tended to occur in those patients with the longest duration of drainage. Postoperative recovery after pleurectomy and thoracic duct ligation was uneventful. We conclude that conservative management of chylothorax will be successful in most cases. Complications of such a policy are fairly common but rarely serious.

Chylothorax after the neonatal period may be traumatic or non-traumatic in origin. Traumatic chylothorax is most commonly associated with surgery for congenital heart disease[1] or in the posterior mediastinum. Other causes may be accidental and trivial, such as coughing, rarely, it may be part of the range of child abuse.[2] Neoplasm, subclavian vein thrombosis, mediastinal lymphangiectasia, and parasitic infection are examples of non-traumatic aetiology

Chylothorax in childhood is a potentially life threatening condition yet sufficiently uncommon to ensure that few centres have much experience in its management. Although many authors recommend a conservative approach,[3] some have advocated consideration of early surgical intervention in cases of traumatic chylothorax.[4] There is therefore some debate about the benefits of surgical as opposed to dietary treatment. We have generally employed the dietary approach, in the form of thoracocentesis, chest drain insertion, and dietary modification, with surgery if this fails We reviewed our last 10 years' experience of chylothorax to establish the effectiveness of this policy and the risks inherent in both medical and surgical treatment.

Patients and methods

Fifteen patients treated for chylothorax between 1976 and 1986 were identified by means of a hospital diagnostic coding index. Patient records were analysed to determine mode of presentation, underlying condition, duration and volume of chyle leak, details of management employed, incidence of complications, and outcome.

Results

The aetiology, management, and outcome for each case are summarised in the Table.

Aetiology. The median age at presentation was 20 months (range 3 months to 9 years) Twelve children had undergone thoracotomy before development of chylothorax, 10 for congenital heart defects. One child had a left lower lobectomy and another resection of an intrathoracic Ewing's sarcoma, followed in both by chyle leakage. Ligation of a persistent ductus arteriosus was the single most common antecedent of chylothorax, which complicates 1% of all such operations in our hospital.

Three patients presented without previous surgery In one of these an upper respiratory tract infection associated with cough seemed to be the precipitating factor and no underlying cause was ever found. The other two patients had abnormalities of the lymphatic system, one had a pleural lymphangioma diagnosed at pleurectomy and the other was a child with Klippel-Trenaunay-Weber syndrome in whom chylothorax followed an attempt to reduce the size of his lymphoedematous leg with occlusive bandages.

Table *Aetiology and outcome in 15 cases of chylothorax*

Age (years/months)	*Sex*	*Precipitating event*	*Maximum chyle loss in 24 hours (ml/kg body weight)*	*Total No of days of drainage*	*Complications*	*Outcome*
3/0	F	PDA ligation	4	26	—	Reaccumulation pleurectomy
0/3	F	PDA ligation	12	12	Low sodium	Resolution
1/6	F	PDA ligation	5	10	Lymphopenia	Resolution
0/7	F	PDA ligation	32	8	Lymphopenia	Resolution
1/8	F	Cavo-pulmonary shunt	9	64	Low sodium, lymphopenia, low albumin, weight loss	Resolution
1/9	M	Cavo-pulmonary shunt	8	15	Low sodium, low albumin	Resolution
0/10	M	Cavo-pulmonary shunt	10	7	—	Resolution
6/0	F	VSD repair	90	11	Lymphopenia	Death
0/11	F	VSD repair, pulmonary artery band	33	7	Lymphopenia weight loss	Resolution
1/4	F	Left Blalock-Taussig operation	86	8	—	Resolution
0/10	F	Left lower lobectomy	12	26	Lymphopenia	Resolution
9/0	F	Ewing's sarcoma	17	7	—	Thoracic duct ligation
6/0	F	Pleural lymphangioma	39	30	Low albumin, weight loss	Resolution, reaccumulation pleurectomy
5/0	M	Klippel-Trenaunay-Weber syndrome	24	29	Weight loss	Resolution reaccumulation pleurectomy
1/9	F	Cough	76	53	Lymphopenia	Resolution

M=male, F=female, PDA=persistent ductus arteriosus, VSD=ventricular septal defect.

Diagnosis. The three children with chylothorax unrelated to surgery presented with a history of increasing shortness of breath over several days. Six of the 12 patients who underwent thoracotomy were diagnosed before they became symptomatic, four because of continuing fluid loss from chest drains inserted at operation and two when pleural effusions were seen on routine postoperative *x* ray films. Chylothorax in six children who had undergone thoracic surgery presented with increasing dyspnoea from two to as many as 50 days postoperatively (median 15 days).

In 12 patients the pleural fluid had a classical milky appearance In three others, before enteral feeding had been restarted after surgery, pleural fluid was serous in nature. The extent to which pleural fluid was subjected to laboratory analysis varied from patient to patient. Diagnosis of chylothorax was made on the basis of a number of factors: clinical history, milky appearance of the fluid, continued sterile effusions, chylomicrons visible on light microscopy, 20–50 leucocytes per high power field, with 90% or more being lymphocytes, and fluid and protein content approaching that of plasma Protein concentration measured in four patients varied from 24 to 55 g/l. All but one effusion was left sided In addition to chylothorax, one patient developed chylopericardium, which required surgical drainage.

Management. All the children were initially managed conservatively from the time of diagnosis. Initial thoracocentesis was always followed by reaccumulation of chyle that necessitated chest drain insertion. Dietary modification was employed in all patients Twelve were given a low fat high protein diet supplemented with medium chain triglycerides (MCT). Typically, this would consist of vegetables, lean meat or white fish, and bread without butter or margarine. Fried foods other than potato chips cooked in MCT oil were excluded as were cakes and biscuits Milk was provided as skimmed milk supplemented with carbohydrate (glucose polymer) and MCT oil. Three children received an elemental diet as their only form of nutrition. Chyle drained from the chest was generally replaced with an equivalent volume of intravenous plasma.

Chyle production. We examined the maximum volume of chyle drained in relation to body weight in any 24 hour period. Three patients were receiving parenteral fluids only postoperatively, yet still drained a mean volume of 42 ml/kg/day over two days. In one patient we opted to substitute total parenteral nutrition for an MCT milk feed that was producing chyle flow around 12 ml/kg/day but found no reduction in the rate of leak over the next 48 hours until we reverted to a low fat enteral diet. The median maximal 24 hour chyle drainage in patients on our standard low fat enteral diet was 17 ml/kg

Outcome. The median duration of chyle leak was 12 days (range four to 64 days) and complications tended to occur in those patients who drained the most chyle (Table) These included loss of more than 8% body weight, hypoproteinaemia, hyponatraemia, and peripheral blood lymphocyte counts that fell two standard deviations below the mean for age.[5]

Discussion

Chyle in the pleural space may compress intrathoracic structures and embarrass respiration. The first line of management is therefore removal of fluid by needle aspiration followed by insertion of an intercostal chest drain should reaccumulation occur. The appearance of the fluid is classically milky but, as three of our cases showed, may be serous if enteral feeding that includes fat is not being given. A protein content similar to the plasma protein concentration and a preponderance of lymphocytes are further evidence that the fluid is chyle. A lipophilic green dye (coal tar dye, Drug and Cosmetic Green no 6) given with a high fat meal will colour chyle, making it distinguishable from other body fluids and may be used as a diagnostic test where doubt persists.[6]

As enteral fat will greatly increase thoracic duct lymph flow[7] most conservative regimens involve a low fat intake. This may be supplemented with medium chain triglycerides (MCT), which are absorbed directly into the portal venous system without forming chylomicrons.[8] Some care should be exercised when using diets high in MCT; essential fatty acid (linoleic acid) deficiency may follow unless linoleic acid, present only in long chain triglycerides, provides at least 4% of energy.

We have tried a number of dietary strategies that involve low fat diet, including supplementation with MCT or parenteral Intralipid (KabiVitrum). We have also used elemental diets that contain most fat as MCT. In our experience, it is not possible to identify any single dietary manoeuvre that is superior in reducing chyle flow. Although total parenteral nutrition might seem to be the logical way to reduce chyle formation, our limited experience suggests that it is not immediately effective. Total perenteral nutrition does, however, provide an alternative method for maintaining adequate nutritional intake and has been used successfully in the management of thoracic diet fistulas by some authors.[9]

The long term complications of conservative management include the secondary effects of chyle loss—namely, nutritional depletion through loss of protein and electrolytes and immune deficiency through loss of immunoglobulins and lymphocytes [10] Despite careful dietary management and the replacement of chest drain losses, one third of our patients lost more than 8% of their body weight or became hypoproteinaemic. One 18 month old baby developed measles while in hospital, despite having no direct contact with an infected child on the ward at the same time, but otherwise there was no clear evidence that patients became immunocompromised.

If severe, the occurrence of such nutritional complications during the course of conservative management is an argument for surgical intervention If chyle leakage seemed undiminished after three weeks of dietary management, or when reaccumulation of chyle followed relaxation of dietary fat restriction, surgery was considered. When diet seemed to be steadily reducing chyle leak we were prepared to continue with our medical management for longer than three weeks. Nine of our patients with chylothorax after thoracotomy and the patient with non-traumatic chylothorax all responded to conservative treatment, although in three this took more than three weeks (four, eight, and nine weeks, respectively). We would not agree, therefore, with Selle *et al* that early surgical intervention should be considered in traumatic chylothorax in children.[4] Both patients with underlying lymphatic disorders and one with chylothorax after persistent ductus arteriosus ligation initially responded to dietary treatment but reaccumulated fluid when dietary fat was increased As the actual point of leakage was impossible to define pleurectomy rather than thoracic duct ligation was successfully employed to prevent further accumulation of chyle within the pleural space. In the case of the child with an intrathoracic sarcoma, chyle leak was noted at the initial tumour resection As duct damage seemed to be the most likely cause at that time, ligation was performed after only one week of failed conservative management.

We conclude that conservative management in the form of chest drainage and low fat diet will lead to successful resolution of most chylothoraces in children When such a policy seems to be steadily reducing chyle leak it may be pursued for weeks or months with the likelihood of success, provided that the nutritional state of the child is well maintained. The risks of nutritional impairment, electrolyte imbalance, and secondary immune deficiency together with the cost of prolonged admission to hospital must be weighed against the risks inherent in further surgery. Failure of conservative management to reduce chyle leak after three weeks or reaccumulation of chylothorax after relaxation of restricted enteral fat intake are indications for surgical intervention. Evidence of underlying lymphatic disorder is probably an indication for earlier rather than later surgical management. If a localised thoracic duct injury is not identified pleurectomy is the surgical procedure of choice.

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Establishment of an intermediate care ward for babies and mothers

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SUMMARY This paper describes one year's experience with the running of a special postnatal ward area, established so that babies who needed more treatment and monitoring than is generally undertaken on postnatal wards but who did not need the facilities of the neonatal unit could be kept by their mother's bedside. This 'intermediate care ward' admitted 297 babies with their mothers during its first year of operation. We estimate that the opening of the ward led to a 20% reduction in admissions to the neonatal unit, without disadvantage to any baby. The indications for admission are outlined and the reactions of patients and staff to the innovation discussed.

It is probably not necessary to admit more than 5% of newborn babies to a neonatal unit, and yet rates of admission are considerably above this in many hospitals. The usual explanation is that the postnatal wards are not considered safe enough, either because they are understaffed or because the midwives on them lack training or interest in neonatal problems. Occasional examples of small babies becoming cold on postnatal wards or of delay in a diagnosis being reached are used to justify a high rate of admssion to the neonatal unit.

Five years ago we began a campaign to decrease the number of admissions to our neonatal unit to reduce mother infant separation and concentrate limited resources on those babies in definite need of intensive care facilities [1] Our initial approach was simply to discuss, on the morning ward round, the reason for each baby's admission to the unit, with a view to seeing if it could safely have been avoided This led gradually to a more critical appraisal of the need for admission by all doctors and nurses involved, and the rate of admission fell from 15% to about 9% over four years. By then it was normal practice for a well baby with a birth weight of 2000 g to be sent to the postnatal ward with his mother. These low birthweight babies, and others with potential problems, were, however, scattered throughout our three postnatal wards and were not necessarily being looked after by midwives with any special expertise For this reason, and to reduce the rate of admission to the neonatal unit further, it was decided to establish a special area on one postnatal ward to which all babies who needed more than average attention could be sent with their mothers We describe our experiences with this 'intermediate care ward' after one year and 297 admissions.

Method

The neonatal unit at St James's University Hospital serves an inborn population of about 4600 each year, as well as being a tertiary referral centre The low birthweight rate among inborn babies is 9%, considerably above the national average of 6·5%. The unit has eight intensive care cots, six high dependency cots, and 18 special care cots. The full time medical staff comprises one consultant neonatologist, one registrar, and four senior house officers. There is always resident middle grade cover for the unit

The intermediate care ward. The ward consists of a six bedded bay, a four bedded bay, two single rooms, and a nursery with space for six cots. It is in close proximity to the nursing station. A fully equipped resuscitaire was provided and a servo-controlled, radiant heated intensive care platform was put in the nursery so that any baby becoming cold on the delivery suite could be efficiently rewarmed. Incubators were available as required from the neonatal unit. The only other additional items of equipment were three electrical thermometers with skin and rectal probes, which could be used to monitor continuously the temperature of the smaller babies.

Staffing. Four of the midwifery staff expressed an interest in establishing and running the intermediate care ward. A short programme of preliminary in service training was provided. This consisted of clinical teaching on the neonatal unit from the neonatal unit sisters, six lectures from the consultant, covering topics such as temperature control, hypoglycaemia, jaundice, nutrition, and the recognition of illness, and attendance at study days for neonatal nurses. These four midwives run the ward area by day, with help from three staff midwives on a three monthly rotation, and the ward area is staffed at night by two staff midwives on three monthly rotations, who also received extra training.

The ward receives more routine attention from the paediatric medical staff than a normal postnatal ward. One of the neonatal senior house officers is responsible for it and performs a daily ward round of all the babies. The senior house officers share this job on a two monthly rotation. The neonatal registrar puts in a daily appearance and, with the consultant paediatrician, conducts a full ward round twice a week.

Admission criteria. Table 1 shows the guidelines used to suggest suitable cases for admission. They are deliberately broad and the final decision on whether a baby should go to the normal postnatal ward, the neonatal unit, or the intermediate care ward is in the hands of the senior house officer on duty.

The nursing expertise and the facilities available on the ward allow the admission of babies who need incubator care, tube feeding, monitoring for hypoglycaemia the management of feeding problems, as in cases of cleft palate, micrognathia, Down's syndrome etc, and phototherapy (available on all postnatal wards). Intravenous infusions are not available and necessitate admission to the neonatal unit.

Table 1 *Guidelines for admission to the intermediate care ward*

Low birthweight babies of more than 1700 g are suitable for admission to the ward as long as there are no signs of illness

Babies with birth weights below the third centile for gestational age are suitable for admission to the ward as long as there are no serious complicating factors and they weigh more than 1700 g

Babies with congenital abnormalities, such as cleft lip and palate or Down's syndrome, are particularly suitable for admission as such babies need to be with their mothers in a supportive environment

Babies of mothers with diabetes are good candidates for admission

Babies with important medical conditions are NOT suitable for admission

Results

A total of 297 babies were admitted to the intermediate care ward during the first year. Table 2 shows these babies classified according to the main indication for admission. The category 'growth retarded appearance but weight >10th centile' describes babies who were underweight for their length and who had wrinkled skin and a paucity of subcutaneous fat.

Altogether, 51 babies (17%) required an initial period of incubator care (mean duration 2·8 days), 81 babies (27%) needed tube feeding (mean duration 6·5 days), and 10 babies received phototherapy

The median duration of admission to the ward was nine days (range one hour to 21 days), and the bed occupancy was about 75%. Sixty babies (20%) remained in hospital for more than 10 days, which is the usual upper limit of stay for obstetric indications. In 293 cases the mother remained with the baby throughout, but in four cases the mother left hospital before the baby and the baby was transferred to the neonatal unit.

Eighteen of the 297 babies were subsequently transferred from the intermediate care ward to the neonatal unit because of medical problems. The diagnoses in these cases are shown in Table 3. Five of the six babies admitted with respiratory symptoms were considered to be asymptomatic when they left the delivery suite, and the indication for admission to the intermediate care ward was low birth weight. The sixth baby (with a birth weight of 2880 g and a gestational age of 39 weeks) had grunting respiration when the decision was made to send him to the intermediate care ward None of these babies needed assisted ventilation and they all did well. Neither of the babies with a low blood glucose concentration detected on screening had symptoms of hypoglycaemia.

Table 2 *Indications for admission among the 297 cases admitted to the intermediate care ward during the first year*

Indication	*No of cases*
Preterm	113 (mean gestation 35 weeks, range 32–36 weeks)
Light for dates	
<10th centile	157 (mean gestation 38 weeks, mean birth weight 2430 g)
<3rd centile	75 (mean gestation 37 weeks, mean birth weight 2110 g)
Infants of mothers with diabetes	25 (four preterm, three <10th centile)
Growth retarded appearance but weight >10th centile	24
Cleft lip and palate	5
Grunting respiration	5
Autosomal trisomy	4 (two Down's syndrome, one Trisomy 1, and one Trisomy 13)

Table 3 *Details of babies admitted to the intermediate care ward who were subsequently transferred to the neonatal unit*

Case No	*Diagnosis*	*Gestation (weeks)*	*Birth weight (g)*	*Age at transfer*
1	Hyaline membrane disease	34	2530	1 h
2	Transient tachypnoea	34	2020	2 h
3	Transient tachypnoea	34	2180	5 h
4	Transient tachypnoea	39	2880	12 h
5	Transient tachypnoea	37	2480	16 h
6	Transient tachypnoea	38	1940	20 h
7	Low blood glucose concentration	38	2540	20 h
8	Low blood glucose concentration	38	2320	2 d
9	Pneumonia	35	2540	3 d
10	Partial trisomy 1	36	3460	6 d
11	Mother went home	35	2190	7 d
12	Poor temperature control	39	2720	7 d
13	Necrotising enterocolitis	35	1980	7 d
14	Ventricular septal defect	40	2640	8 d
15	Trisomy 13	36	2260	8 d
16	Patent ductus arteriosus	37	2460	9 d
17	Mother went home	36	1900	10 d
18	Unwell (? infected)	36	2310	10 d
19	Mother went home*	37	1980	11 d
20	Mother went home*	37	1900	11 d
21	Abdominal distension	35	2100	13 d
22	Infected umbilicus	36	2160	14 d

*=Twins

Table 4 *Change in admissions to neonatal unit before and after opening of the intermediate care ward. Values are No/Total and (percentage)*

Birth weight group (g)	*Admission rate in year before ward opened*	*Admission rate in year after ward opened*
1700–2000	41/55 (74)	40/72 (55)
2001–2500	94/260 (36)	59/255 (23)
>2500	195/4243 (5)	140/4176 (3)
Total >1700	330/4558 (7)	239/4503 (5)

The rate of admissions to the neonatal unit in the year preceding the opening of the intermediate care ward and in the following year are shown in Table 4. It is not possible to prove that the reduction in admissions was the result of opening the ward, but among babies weighing more than 1700 g the rate of admission fell from 7·2% to 5·3% between these years. This represents about 85 babies each year, which is a 20% reduction in admissions to the neonatal unit.

Discussion

At the end of its first year of operation the intermediate care ward was popular with everyone.

The mothers appreciate it because of the greater involvement they have with their babies. We have not attempted a formal evaluation of parental response, but the fact that nearly all the mothers were prepared to stay longer in hospital than they needed to from their own obstetric point of view seems a good indicator of the attractiveness of the situation, especially as our population tends to the opposite extreme when the baby is admitted to the neonatal unit. The atmosphere on the ward always seems a happy one and there is a good deal of mutual support between the mothers, which has been commented on by many of them.

The midwives are enthusiastic because they like the close participation with mothers and their new babies and think that it gives them greater scope to develop their skills effectively than the usual hurly-burly and rapid turnover on a postnatal ward. None of them wants to be a full time neonatal nurse, and it seems that we have found a niche for certain midwives who no doubt exist in other hospitals too. The ward also provides a good opportunity for training student midwives in neonatal special care, which may be more appropriate to their needs than training in intensive care on a neonatal unit.

The neonatal nurses value the ward because it has relieved them of a group of babies who do not really need their highly developed skills. This aspect is particularly important at a time when most neonatal units are desperately short of nurses with training and experience in intensive care. When sick babies are denied admission to the unit because the staff are diverted by hordes of babies who need little more than tube feeding then clearly something is wrong. Our conclusion that some 85 babies were spared admission to the neonatal unit must be seen in the context of our already low rate of admission Hospitals with higher rates of admission could expect correspondingly greater reductions.

The junior doctors like the intermediate care ward because of the air of enthusiasm for a paediatric input, which is not always found on postnatal wards, and because of the sense of participation and continuity that it offers them. They also have the security of knowing that all the babies likely to cause problems are in one place and well supervised. As admission to the ward does not entail separation of mothers and babies there is no pressure to avoid admission, other than the availability of beds. Clearly, the babies on the intermediate care ward demand more attention from the neonatal senior house officers than most of the other babies on postnatal wards. These babies, however, would need attention wherever they were.

The paediatric consultant likes the ward because it is an oasis away from the problems on the neonatal intensive care unit and because it is a good place for teaching everyday aspects of baby care to new senior house officers, medical students, and student midwives.

The babies benefit by having fewer caretakers than they would if admitted to the neonatal unit, by being exposed to fewer pathogenic microorganisms,[2] and by being at less risk of unnecessary medical investigation or treatment. We do not feel that any baby has been disadvantaged by admission to the intermediate care ward rather than to the neonatal unit. In particular, there were no instances of symptomatic hypoglycaemia among light for dates babies, and we agree with Jones and Roberton that such babies no longer deserve their reputation for causing problems in the neonatal period.[3] As an admission criterion 'grunting respiration' contravened the guidelines, and although four of the five babies admitted on this indication settled rapidly we recommend that babies with respiratory symptoms are admitted directly to the neonatal unit.

Although we believe that health authorities should fund an increase in midwifery establishment to support the innovation that we describe, we have had to service our intermediate care ward from within the existing establishment. This is just possible because there is no change in the number of babies cared for or in the nature of their problems, simply a relocation. Given willingness to allocate staff according to the workload, it ought to be a feasible proposition in most hospitals. The ward was closed for two weeks during the year. This was in a period of drastic staff shortage, during which other postnatal ward beds were also closed. Now that the advantages of the ward are well established every effort is made to grant it a privileged status among the postnatal areas.

The intermediate care ward that we have established would probably not be feasible, or indeed desirable, in every other hospital, either in concept or in detail. Many hospitals have addressed the problem of unnecessary admissions to the neonatal unit in other ways. None the less, in some hospitals far too many well babies are admitted to the neonatal unit, while their mothers go to the postnatal ward. There is no excuse for failing to make efforts to avoid this and we hope that our experience may be an encouragement and a guide for some.

We thank the midwives, whose enthusiasm for the project was so vital to its success

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The idiopathic hypereosinophilic syndrome

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SUMMARY A 14 year old girl with idiopathic hypereosinophilic syndrome is described. In addition to weight loss, anaemia, amenorrhoea, general lethargy, anorexia, mouth ulcers, blisters of hands and feet, and petechial skin rash, she had features of involvement of the cardiovascular system as the major complication. She responded well to treatment.

After a comprehensive search of the published reports 18 cases of this syndrome were identified in children under 16 years. Fifteen of these children had involvement of the cardiovascular system as the major source of their morbidity and mortality. Summary of the clinical details and laboratory, biopsy, and necropsy findings of the involvement of the various organ systems of the 18 children is presented.

Hypereosinophilia of over $1\cdot5\times10^9$/l accompanies various diseases. In some cases no cause can be found and the hypereosinophilia may be accompanied by multiple organ involvement, especially of the cardiovascular system, with high morbidity and mortality. The idiopathic hypereosinophilic syndrome is primarily a disease of middle age, but an occasional case has been encountered in children.

Case report

A 14 year old white girl presented six weeks after an illness that lasted 10 days, in which she had developed mouth ulcers and blisters of the hands and feet. These had settled spontaneously, but the lethargy, nausea, and anorexia had persisted, and she had complained of aching limbs. She had described symptoms of increasing dyspnoea on minimal exertion and orthopnoea and developed a fine petechial rash two days before presentation Her menses, which had started a year earlier, had stopped during the illness

She had had asthma for two years, which was controlled with regular inhalations of beclomethasone and occasional inhalations of salbutamol. She was allergic to feathers There was no recent infectious or relevant travel history.

On examination she was unwell, with a temperature of 38°C, pulse rate 128 beats/minute, regular, respiratory rate of 28/minute, blood pressure 130/100, weight 46 kg (25th centile), and height 163 cm (60th centile). There was a sparse petechial rash on the upper trunk and upper arms, with splinter haemorrhages under her fingernails, and the pulps of her fingertips were tender on palpation She was in congestive heart failure, with clinical evidence of a pericardial effusion. A grade 2/4 pansystolic murmur radiated from the apex to the axilla There was no lymphadenopathy or splenomegaly, but the liver was enlarged, 2 cm below the costal margin at the mid-clavicular line, and tender.

Investigations. Her haemoglobin concentration was 9·3 g/dl, mean corpuscular volume 78·7 fl, mean corpuscular haemoglobin 26·7 pg, platelets 315×10^9/l, white blood cells $13\cdot4\times10^9$/l (neutrophils 45%, lymphocytes 15%, monocytes 1%, and eosinophils 39% ($5\cdot2\times10^9$/l), showing partial degranulation), and erythrocyte sedimentation rate 66 mm in the first hour. The prothrombin and kaolin cephalin clotting times were normal. Bone marrow biopsy and trephine examination showed a hypercellular marrow with pronounced eosinophilia but no evidence of malignancy. Chest *x* ray film showed considerable cardiac enlargement, with a globular shaped heart, pulmonary oedema with vascular redistribution, and a small right sided pleural effusion. M mode and 2D echocardiography showed a large pericardial effusion and areas of increased echodensity in the region of the apex of the left ventricle and the posterior leaflet of the mitral valve, suggesting endocardial thickening. An electrocardiogram (ECG) showed sinus tachycardia

The serum electrolytes, glucose, and liver function tests yielded normal results except for a low albumin concentration (32 g/l) and slightly raised lactate dehydrogenase activity (351 IU/l (normal 100–300 IU/l)). Serum concentrations of vitamin B_{12}

were 501·3 ng/l (normal 180–710 ng/l), of folate were 2·2 µg/l (normal >2·5 µg/l), and of ferritin were 70 ng/ml (normal 10–64 ng/ml). Protein electrophoresis (in g/l) showed total protein 52, albumin 25, globulins 37, (alpha$_1$ 4 (normal 2–4), alpha$_2$ 10 (5–8·5), beta 7 (7–11), and gamma 16 (8–16)), IgG 19·22 (7–19), IgM 1 (0·50–2·2), and IgA 0·93 (0·9–4·5). Serum total IgE concentration was 154 KU/l (normal <70·3 KU/l), functional CH50 3·25 min (1·82–3·62), C3 209 mg/dl (70–160), C4 29 mg/dl (10–30) properdin factor B 53·1 mg/dl (20–50), and C reactive protein 0·61 mg/dl (<0·6). Rheumatoid factor was 240 IU/ml (<15). Antibodies for nuclear, mitochondrial, smooth muscle, parietal, canalicular, glomerular, and reticulin were negative. Anti-double stranded deoxyribonucleic acid (DNA) binding capacity was 0·9 mg/l (normal <5 mg/l).

Serial blood cultures and faeces examination, throat swab, Paul-Bunnell test, and tests for viral titres, hepatitis B surface antigen, and hepatitis A IgM yielded negative results. Antistreptolysin O was <100 Todd Units and antistreptococcal deoxyribonuclease B 1/75 (upper limit 1/200). Antibodies to cysticerci filaria, fasciola, hydatid disease, toxocara, toxoplasma, *Aspergillus fumigatus, Micropolyspora faeni* and *Thermoactinomyces vulgaris* were negative. Tests on urine samples showed protein 3+, white blood cells <1/HPF, few granular casts and large number of epithelial cells and mucus, no growth, and a 24 hour protein excretion of 0·3 g. Her karyotype was normal.

On the basis of the clinical syndrome, eosinophilia without a recognisable cause, and the echocardiogram findings, a diagnosis of idiopathic hypereosinophilic syndrome was made. She was begun on treatment with prednisolone 2 mg/kg/day, frusemide, and folic acid, and was anticoagulated with warfarin.

The signs of congestive heart failure improved appreciably within two days and the petechial rash disappeared within three days The eosinophil count returned to normal within two days The erythrocyte sedimentation rate, lactate dehydrogenase activity, rheumatoid factor, and serum IgE and folate concentrations returned to normal. The endocardial echoes and pericardial effusion decreased within a few days of beginning treatment and had completely disappeared within three months. Signs of mild mitral regurgitation confirmed by Doppler ultrasound persisted.

After her dramatic clinical improvement the steroids were gradually withdrawn and were stopped after six weeks. She then developed mild bronchospasm on excitement, which responded to inhaled salbutamol with concomitant improvement in the peak flow rate and forced expiratory volume in one second/forced vital capacity percentage, and was restarted on inhaled beclomethasone. Within two weeks of stopping oral steroids her eosinophil count increased to 1·5×10^9/l, and her total white blood cell count was 8·0×10^9/l. She was restarted on prednisolone at a dose of 10 mg on alternate days, after which the eosinophil count returned to normal. She remains anticoagulated with warfarin.

Discussion

Eosinophilia. Eosinophilia is the term applied to an increase in the total blood eosinophil concentrations. In normal individuals living in the United Kingdom the blood eosinophil count is less than 0·55×10^9/l. The practice of referring to eosinophil concentrations as 'percentages' may be misleading and absolute figures (×10^9/l) should be used. Usually, the presence of eosinophilia has no detrimental effect on the body and there is evidence that it may have a role in the body defence mechanisms. It accompanies many disease states, mainly allergic and parasitic (Table 1), or it can be an incidental finding, but occasionally patients with eosinophilia are found to have one of the more serious and rarer causes, such as Hodgkin's disease.[1] Treatment of the primary disease will usually resolve the eosinophilia.

Hypereosinophilia. Hypereosinophilia is the term applied empirically when the blood eosinophil count

Table 1 *Some recognised causes of eosinophilia All disorders mentioned might cause hypereosinophilia Those that might be associated with a very high eosinophil count are underlined*

1 Allergic disorders asthma, hay fever, allergic rhinitis, urticaria, eczema, pulmonary aspergillosis
2 Drug reactions
3 Parasitic infestations visceral larva migrans (toxocariasis), trichinosis, ascariasis, hookworm disease, strongyloidiasis, filariasis (tropical eosinophilia), schistosomiasis, hydatid disease, malaria
4 Skin disorders eczema, dermatitis herpetiformis, exfoliative dermatitis, psoriasis, pemphigus
5 Infections brucellosis, scarlet fever, acute infectious lymphocytosis, infections due to mycobacteria, chlamydia, cytomegalovirus, and *Pneumocystis carinii*
6 Haematological Fanconi's anaemia, thrombocytopenia with absent radii, post-splenectomy
7 Neoplastic disorders Hodgkin's disease, lymphosarcoma, leukaemia, carcinoma of lung and gut
8 Connective tissue/vasculitis/granulomatous disorders, especially those involving the lungs polyarteritis nodosa, Churg-Strauss syndrome, rheumatoid arthritis, systemic lupus erythematosis, scleroderma, cryptogenic pulmonary eosinophilia
9 Immune deficiency disorders congenital immune deficiency syndromes, hyper-IgE with infections
10 Miscellaneous, liver cirrhosis, radiation treatment, Crohn's disease, ulcerative colitis, peritoneal dialysis, congenital heart disease, familial eosinophilia (autosomal dominant), idiopathic hypereosinophilic syndrome (including eosinophilic leukaemia)

is $1\cdot5\times10^9$/l or higher. Some disorders usually give rise to counts above $1\cdot5\times10^9$/l,[1]—for example, drug reactions, intrinsic asthma (a surprising fact compared with patients with extrinsic asthma, in whom the eosinophil count is usually below 1×10^9/l), parasitic diseases, vasculitis and granulomatous diseases, and neoplasms. Certain other diseases are associated with striking eosinophilia: leucocyte counts of 30×10^9/l–100×10^9/l or higher may be seen where 50–90% of the blood leucocytes may be eosinophils. Diseases that are more commonly associated with such high counts are underlined[2] in Table 1, but in general any of the disease processes mentioned in the Table—that is, any cause of eosinophilia—may be associated with hypereosinophilia of whatever degree.

Hypereosinophilia can be primary. This may be an isolated finding. On the other hand, it might be associated with organ system dysfunction of varying extent and severity, the cardiovascular and nervous system and skin being most commonly involved—the idiopathic hypereosinophilic syndrome.

The idiopathic hypereosinophilic syndrome. In 1968 Hardy and Anderson drew attention to the fact that persistent hypereosinophilia of any type could be associated with a range of similar complications and they grouped these together as the hypereosinophilic syndrome.[3] Chusid *et al* confirmed this in 1975 but restricted the diagnosis of hypereosinophilic syndrome to patients in whom no underlying cause for the hypereosinophilia could be shown,[4] so that the term idiopathic hypereosinophilic syndrome is applied when the following criteria are fulfilled:

(1) Eosinophilia $\geqslant1\cdot5\times10^9$/l;
(2) Persists for at least six months or fatal in a shorter time;
(3) Results in organ system dysfunction;
(4) Absence of a recognised cause for the eosinophilia.

The term encompasses various diagnostic terms applied previously to a range of cases with almost similar natural history, physical findings, laboratory data, and autopsy findings, including eosinophilic leukaemia, disseminated eosinophilic collagen disease, and Loeffler's fibroplastic endocarditis with eosinophilia. The condition called eosinophilic gastroenteritis is probably part of the wide range of this syndrome.[5]

The idiopathic hypereosinophilic syndrome has a wide range of severity with at least three different forms. Some patients only have hypereosinophilia with lung involvement and angio-oedema. Others present with (or develop) severe cardiac and central nervous system complications. A third group have eosinophil cytogenic abnormalities and other features of a leukaemic disease, characterised as eosinophilic leukaemia. Occasionally, the second form terminates as a blast cell leukaemia.[6] Hypereosinophilia as an isolated finding is not considered to be a subgroup of this syndrome and probably has no special clinical relevance, although the patient will require regular reviews to exclude an occult underlying disease process.

Aetiology
Several theories have been put forward to explain the idiopathic hypereosinophilic syndrome. Some authors have claimed that it is an autoimmune disease.[7] It is also possibly of a neoplastic nature.[8] Parrillo *et al* showed a variety of immunological abnormalities in the patients they studied.[9] In most of the cases described by Spry *et al* the findings suggested that a parasitic or allergic disease had preceded the onset of hypereosinophilia, and some had high serum IgE concentrations.[10] These findings raised the possibility that an initial eosinopoietic stimulus may lead to a late and exaggerated response, which persists. Carey *et al* reported a case of transient hypereosinophilia in an infant of a mother with this syndrome and suggested that the infant's hypereosinophilia could be a response to an eosinophilia producing factor by the mother, with transplacental transfer.[11]

A definitive cause for this syndrome, however, has not been identified, but perhaps understanding the factors that influence the production and distribution of the eosinophil and the mechanisms of tissue damage might give some insight into its aetiology.

Factors that influence blood and tissue eosinophil concentration. Eosinophils normally constitute a small proportion of the circulating leucocytes. A diurnal variaton that is the converse of the variation in plasma corticosteroid concentrations occurs, with blood eosinophilia peaking at night. The production of the eosinophil in the bone marrow is under the control of the T lymphocytes. Lymphocytes also produce factors that are chemotactic for eosinophils. Once eosinophils are released from the marrow they circulate in the blood only briefly, with a half life of six to 12 hours. They leave the blood stream and are distributed in tissues where they persist for at least several days, being a tissue dwelling cell. They are most abundant in those tissues with epithelial surfaces exposed to the environment, including the gastrointestinal tract, the skin, and the upper respiratory tract.[12]

Apart from the lymphocytes, several other factors may influence eosinophil concentrations in blood and tissue. On triggering and degranulating the mast

Table 2 *Summary of clinical, biopsy, and necropsy findings of 19 children with the idiopathic hypereosinophilic syndrome*

Author (year)	*Age at onset (years)*	*Sex*	*Presenting symptoms*	*Cardiovascular system*	*Nervous system*	*Skin/muscle/joints*	*Renal*	*Pulmonary*	*Gastrointestinal tract*	*Hepatic*
Bentley (1951)[15]	5	M	Fever, macular rash, petechial rash, coma	*Postmortem examination* Myocardial petechiae and scarring, mural thrombus in left ventricle	Coma, decorticate posture *Cerebrospinal fluid* No abnormality *Postmortem examination* Myeloblastic infiltration of meninges and brain	Macular and petechial rash Subcutaneous nodules over parietal bones *Biopsy* Lymphoid and eosinophil infiltration	*Postmortem examination* Petechiae in both kidneys Blast cells infiltration of kidneys and bladder	Dry cough *Chest x ray* Lung infiltrates *Postmortem examination* Haemorrhagic areas Pulmonary oedema and myeloblast infiltration	*Postmortem examination* Stomach dilatation Petechiae all over gastrointestinal tract	Hepatomegaly *Postmortem examination* Blast cells infiltration
Chusid (1975)[4]	5 5	M	Periodic attacks of fever, rash, diarrhoea, and angio-oedema	None	Abnormal electroencephalogram	Rash, angio-oedema *Skin biopsy* Perivasculitis, eosinophil infiltration	Mild to moderate intermittent proteinuria	Transient infiltration	None	*Biopsy* Eosinophilic triaditis'
De Vaan (1979)[16]	1	F	Refusing to walk or stand	Gallop rhythm and sinus tachycardia *Postmortem examination* Endocardial thickening of left atrium and subendocardial fibrosis with iron pigment deposition in myocardium of both ventricles and left atrium. Coronary thrombosis Eosinophil infiltration including blast cells in myocardium	None	Refusing to walk or stand *Skin biopsy* Papillomatosis and scattered mature eosinophil infiltration and hyperkeratosis *Muscle biopsy* Some focal atrophy, no eosinophil infiltration	*Postmortem examination* Eosinophil infiltration including blast cells	Pneumonia *Post mortem examination* Increase in weight of lungs Vascular thrombi Areas of red blood cell extravasation fibrin in alveolar spaces, and formation of hyaline membranes Macrophages and eosinophils in alveolar spaces	None	Hepatomegaly *Biopsy* Diffuse eosinophil infiltration *Postmortem examination* Enlarged, eosinophil infiltration including blast cells
Donohoe (1950)[17]	7	M	Joint pains and fever	Congestive heart failure cardiomegaly, mild hypertension systolic murmur, mitral regurgitation	None	Subcutaneous oedema, arthralgia	None	Bilateral basal crepitations	None	Hepatomegaly
Engbaek (1942)[18]	7	M	Headaches, fever neck stiffness, and arthralgia	Congestive heart failure cardiomegaly *Postmortem examination* Hypertrophy dilatation and parietal thrombus in both ventricles and myocardial scarring Dilatation of coronaries	Not described	Not described	Not described	*Postmortem examination* Lungs indurated, cyanotic, mottled and inflamed Thrombi oedema, and eosinophil infiltration	Not described	None
Engfeldt (1976)[7] Case 1	8	M	Fatigue anorexia, abdominal pain, vomiting dyspnoea cough pains in back and neck	Terminal acute heart failure *Postmortem examination* Biventricular hypertrophy, thrombus in right auricle and ventricle Endo-, myo-, and pericardial scarring and inflammatory cells infiltrate mainly eosinophils	*Electroencephalogram* Dysrhythmic	Pains in back and neck *Postmortem examination* Eosinophil infiltration of muscle	Moderate albuminuria, hyaline casts, and red blood cells in urine. Uraemia *Postmortem examination* Eosinophil infiltration of kidneys	Dyspnoea, cough *Chest x ray* Peribronchial thickening and pleural effusion *Postmortem examination* Eosinophil infiltrate	Abdominal pain and vomiting	Hepatomegaly *Post mortem examination* Eosinophil infiltration
Case 2	10	M	Headaches, fever, rash hyperkeratosis, and scaling of face arms, and legs pronounced alopecia, conjunctivitis, myalgia	Cardiomegaly apical systolic murmur	None	See presenting symptoms Subcutaneous oedema and redness over wrists and knees Arthralgia *Biopsy of skin and muscle* Inflammatory cells, especially eosinophils and plasma cells Non-specific changes in small blood vessels thrombosis and endarteritic changes	Slight proteinuria	Atelectasis of right middle lobe Pleural effusion	None	Hepatomegaly
Foamc (1964)[19]	6 7	F	Sore throat Tuberculosis over previous 12 months, on isoniazid, rifampicin, ethambutol	Congestive heart failure, cardiomegaly hypertension *Echocardiogram* Dilated left ventricle and left auricle *Catheterisation* Left ventricular lumen was reduced	Not described	Ulceration of finger tips Swelling of right sternocleidomastoid *Skin biopsy* Perivascular inflammatory cell infiltration *Muscle biopsy* Endothelial thickening and alteration of media no perivascular inflammation	Macroscopic haematuria *Biopsy* Focal glomerulonephritis	Pulmonary hypertension and oedema	Not described	Hepatomegaly

Continued

Lymph nodes/spleen	*Total white blood cell count (×10⁹/l) at presentation*	*Eosinophil count (×10⁹/l) at presentation*	*Haemoglobin (g/dl) at presentation*	*Platelets (×10⁹/l) at presentation*	*Peripheral blood white blood cell morphology*	*Bone marrow*	*Other laboratory findings*	*Duration*	*Treatment*	*Authors' diagnosis*
Splenomegaly Generalised lymphadenopathy *Post-mortem examination* Blast cells in lymph node and spleen	185	157 25	8	60	64% Polymorphonuclear eosinophils 17% eosinophil metamyelocytes 3 4% eosinophil myelocytes	Initially eosinophil hyperplasia Terminally an increase in myeloblastic forms (85 3%)	—	7 months	Cortisone then busulphan then cortisone radiation to lungs and 6-mercaptopurine	Eosinophilic leukaemia
Lymphadenopathy during attacks *Lymph node biopsy* Hyperplastic germinal centres Increased eosinophils	35-7	21 42	11 3	400	Most primitive cell in the circulation was eosinophil myelocyte No morphological abnormality of eosinophils	Not described	Raised IgE	Reported alive 5 5 years after presentation	Prednisone on alternate days increasing to daily during attacks	Idiopathic hypereosinophilic syndrome manifesting as periodic attacks of fever malaise angio-oedema and hypereosinophilia
Generalised lymphadenopathy and splenomegaly *Lymph node biopsy* Follicular hyperplasia and some eosinophils in blood vessels *Postmortem examination* Enlarged spleen and mesentric lymph node Eosinophil infiltration including blast cells in both	49-9	19 96	7	63	Neutrophils Myelocytes 1% metamyelocytes 2%, band forms 4%, segmented 28% Eosinophils 40% band and segmented forms no younger forms Lymphocytes 23% Monocytes 1% Plasma cells 1%	Hypercellular Some disrupted unidentifiable cells seemed to originate mainly from eosinophil series Increase in eosinophil series at all maturation stages Later on, decrease in megakaryocytes	Coombs and IgE normal IgG and IgM raised Latex and antinuclear factor −ve "Rose" test +ve Serum folate low normal Serum vitamin B_{12} raised	3 months	Prednisolone 6-mercaptopurine	Eosinophilic leukaemia or a variant of juvenile chronic myeloid leukaemia
Cervical lymphadenopathy, splenomegaly	22 1	10 387	8 8	200	Eosinophils deficient in granules	Blast forms 53% myeloblasts 0 5%, eosinophil myelocytes 2 5% eosinophil metamyelocytes 2 5% juvenile eosinophils 2 5%, adult eosinophils 7 5%	—	Reported alive 12 years later ? Any treatment	Adrenocorticotropic hormone Eosinophils increased twice on its withdrawal	Eosinophilic leukaemia
Postmortem examination Splenomegaly Eosinophil infiltration of lymph node and spleen	101 2	78 936	Not described	Not described	Eosinophils of mature type Variable size, number, and distribution of granules 2–3 lobed nuclei	Very cellular with enormous increase in eosinophils, especially lobulated forms	—	11 weeks	—	Eosinophilic leukaemia
Lymphadenopathy and splenomegaly *Postmortem examination* Eosinophil infiltration of spleen and mediastinal lymph node	113	79 1	Normochromic anaemia	Normal	Mature eosinophils initially Later on, more immature forms	Initially Proliferation of granulocytes and numerous myelocytes, mainly eosinophils Later 40% Mature eosinophils, 60% undifferentiated cells and very few erythroblasts, neutrophils, myelocytes, or metamyelocytes	Increased gammaglobulin, decreased albumin Wassermann reaction and lupus erythematosus cell −ve Heterophile antibodies −ve	8 months	Adrenocorticotrophic hormone	Disseminated eosinophilic collagen disease
Generalised lymphadenopathy	21 7	10 85	10 8, normocytic anaemia	Normal	Mature eosinophils	Hypercellular 30% Of myeloid series were eosinophils	Decreased serum albumin, pronounced hypergammaglobulinaemia Wassermann reaction, heterophil antibody Coombs, and lupus erythematosus cell −ve	Reported well 22 months later	Adrenocorticotrophic hormone, twice weekly Lowering of dose was followed by relapse	Disseminated eosinophilic collagen disease
Not described	12	4 8	Normal	Normal	—	Several blast cells which disappeared later on	Autoimmune, antinuclear factor and circulating immune complexes −ve IgE normal	3 years 6 months	Diuretics, digitalis, and steroids	Idiopathic hypereosinophilic syndrome

Continued

Table 2 *Summary of clinical, biopsy, and necropsy findings of 19 children with the idiopathic hypereosinophilic syndrome (continued)*

Author (year)	*Age at onset (years)*	*Sex*	*Presenting symptoms*	*Cardiovascular system*	*Nervous system*	*Skeletal muscle/joints*	*Renal*	*Pulmonary*	*Gastrointestinal tract*	*Hepatic*
Gol[illegible] (1952)[20]	7	M	Fever Pain in abdomen and right axilla	None	None	None	None	None *Chest x ray* No abnormality	None	None
Herrera-Gocpfert (1985)[21]	9	M	Myalgia, arthralgia, fever delirium facial and leg oedema progressive dyspnoea	Congestive heart failure, cardiomegaly systolic murmur (mitral regurgitation). *Postmortem examination* Ventricular dilatation and hypertrophy Thrombi in auricle and right ventricle Extensive subendocardial fibrosis Thrombosis and inflammatory cell infiltration by lymphocytes plasma cells and eosinophils in blood vessels of myocardium	None *Postmortem examination* Cysticercus in left putamen thought to be an incidental finding	Myalgia arthralgia *Muscle biopsy* Nonspecific	Not described	*Chest x ray* Infiltrative pulmonary changes *Postmortem examination* Thrombi infarcts and inflammatory cells infiltration by lymphocytes plasma cells and eosinophils in blood vessels of lungs	Not described	Hepatomegaly *Postmortem examination* Eosinophil infiltration
Knott (1938)[22]	7 5	F	Fever, sore throat, pains in feet, anorexia Irritability	Acute heart failure. Cardiomegaly systolic murmur (mitral regurgitation) *Postmortem examination* Left atrium greatly dilated Ventricles enlarged endocardial and myocardial fibrosis, especially of left. Endocardial fibrosis immediately under the posterior leaflet of mitral valve extending into chordae tendineae Destruction of posterior leaflet of mitral valve Arterial emboli in right leg	Extensive involuntary choreiform hyperkinesia pronounced hypotonia absent abdominal reflexes	Pains in feet. Generalised coarse brown/macular rash Erythema annulare Joints normal	*Urine* Numerous epithelial cells, no other abnormality	Attacks of bronchopneumonia dyspnoea and wheezing associated with cardiac decompensation *Postmortem examination* Lung oedema Pneumonic changes with eosinophil infiltration	None	Hepatomegaly
Libanoff (1976)[23]	9	M	Dizzy spells fatigue, shortness of breath	Congestive heart failure, cardiomegaly systolic murmur (mitral regurgitation). *Postmortem examination* Extensive endocardial and myocardial fibrosis in both ventricles most severe at the apical position of right ventricle A anterior leaflet of mitral valve was destroyed Pericardial effusion No eosinophil infiltrate	None	None	None	Dyspnoea *Chest x ray* Increased vascular markings *Postmortem examination* Pleural effusion	*Postmortem examination* Ascites	Hepatomegaly *Postmortem examination* Liver congestion
Olson (1982)[24]	9	M	Fatigue anorexia, weight loss fever cough	Congestive heart failure cardiomegaly systolic murmur (mitral regurgitation) *Postmortem examination* Biventricular endomyocardial fibrosis (mural thrombi in left ventricle	Not described	*Skeletal muscle biopsy* Normal	Not described	Cough *Chest x ray* Bilateral alveolar pneumonitis *Biopsy* Hypersensitivity pneumonitis	Not described	Clinically not described *Postmortem examination* Chronic passive congestion and centrilobular necrosis
Rasche (1973)[25]	5	F	Abdominal pain diarrhoea vomiting fever	Congestive heart failure cardiomegaly. *Postmortem examination* Biventricular dilatation, thrombi in both ventricles and right atrium, containing abundant eosinophils Coronary thrombosis and myocardial necrosis	Irritability confusion restlessness coma *Postmortem examination* Thrombi in cerebral arterioles and venules necrosis in thalamus and cerebellum	None	Normal serum creatinine and urea *Postmortem examination* Focal proliferative glomerulitis	Dyspnoea *Chest x ray* Linear opacities in both bases *Postmortem examination* Red and congested Vascular thrombosis and lung infarct	Abdominal pain, diarrhoea and vomiting	Hepatomegaly Prolonged prothrombin time *Postmortem examination* Thrombi in sinusoids and eosinophil infiltration

Continued

Lymph nodes/spleen	*Total white blood cell count (×10^9/l) at presentation*	*Eosinophil count (×10^9/l) at presentation*	*Haemoglobin (g/dl) at presentation*	*Platelets (×10^9/l) at presentation*	*Peripheral blood white blood cell morphology*	*Bone marrow*	*Other laboratory findings*	*Duration*	*Treatment*	*Authors' diagnosis*
Splenomegaly Generalised lymphadenopathy Tender lymph node in right axilla *Lymph node biopsy* Eosinophil and polymorph infiltration Fibrosis In general, picture is of lymphadenitis, no other specific changes, no parasites and no calcification	38 3	19 9	Moderate anaemia'	Not described	Neutrophil band forms 3% segmented forms 31% Eosinophil segmented forms 52% Lymphocytes 13% Monocytes 1% Normal granules in eosinophils	Pronounced increase in eosinophils Otherwise normal	Wassermann reaction −ve Mantoux test 1/1000 +ve Globulin and albumin normal	When last seen 7 months later was well and attending school but generalised lymphadenopathy leucocytosis (19 6×10^9/l), and eosinophilia (2 35×10^9/l) had persisted On repeated examination of blood stools and urine during the above period no parasites were seen	None The fever splenomegaly and anaemia disappeared spontaneously	Eosinophilia infectiosa
Generalised lymphadenopathy *Lymph node biopsy* Non-specific *Post-mortem examination* Spleen and lymph node enlarged Eosinophil infiltration	Not specified	Not specified	Not described	Not described	At some stage white blood cell count was 85×10^9/l, with 75% eosinophils of normal morphology	Increased eosinophils of normal morphology *Post-mortem examination* Increased eosinophils (98%)	Total serum protein 82 g/100 ml, inversion of albumin/globulin ratio Latex test, lupus erythematosus cells and antinuclear factor −ve	6 months	Not described	Idiopathic hypereosinophilic syndrome
Generalised lymphadenopathy Splenomegaly	27	18 3	Hypochromic anaemia	Not described	Neutrophils segmented 13% band forms 3% metamyelocytes 1% Eosinophils segmented 54% band forms 13% myelocytes 1% Monocytes 2% Lymphocytes 13%	Hypersegmentation of the neutrophils Pronounced eosinophilia Eosinophils 13 5% eosinophil precursors 20% Mature eosinophils show degranulation No evidence of leukaemia	Direct Coombs test −ve Albumin reduced Alpha$_1$ and alpha$_2$ and gammaglobulins raised	10 5 months	Initially thought to be rheumatic fever penicillin Glutisal (salicylamide + ethenzamide) and Nirvanol (a hydantoin) with some improvement Later cortisone (5 days)	Fibroplastic parietal endocarditis with blood eosinophilia
Splenomegaly *Post mortem examination* Spleen congestion	188 5	169 65	10 2	120	—	Increase in eosinophils at myelocyte metamyelocyte and segmented cells level Slight increase in plasma cells	Albumin and globulin normal	3 years	Not described	Eosinophilic leukaemia
Clinically not described *Postmortem examination* Lymph node and spleen showed extramedullary haematopoiesis	55	48 4	Not described	Not described	Mature eosinophils	Initially eosinophil hyperplasia without an increase in immature forms *Second biopsy* Hypercellularity and increased myeloblasts (7%)	Rheumatoid factor −ve	10 months	Diethyl carbamazine with no improvement Prednisone	Hypereosinophilic syndrome preleukaemic state
Splenomegaly *Post-mortem examination* Splenic infarcts Eosinophil infiltration of lymph node and spleen	152	130 72	8 1	195	8% Segmented neutrophils 1% neutrophil band forms 5% lymphocytes 83% eosinophils 2% eosinophil band forms 1% eosinophil myelocytes	Myelocyte Erythrocyte ratio=20 1 Predominant cells were eosinophil myelocytes metamyelocytes and mature eosinophils *Post-mortem examination* Hyperplasia of eosinophil series with orderly maturation	Lupus erythematosus cell −ve Total serum protein protein electrophoresis and immunoglobulin normal	25 days	Digitalis antibiotic steroids	Acute rapidly fatal case of Loeffler's endocarditis

Continued

Table 2 *Summary of clinical, biopsy, and necropsy findings of 19 children with the idiopathic hypereosinophilic syndrome (continued)*

Author (year)	*Age at onset (years)*	*Sex*	*Presenting symptoms*	*Cardiovascular system*	*Nervous system*	*Skin/muscle/joints*	*Renal*	*Pulmonary*	*Gastrointestinal tract*	*Hepatic*
Spry (1983)[10]	14	M	Diarrhoea, fever, sweating, abdominal pain	None	None	None	None	None	Diarrhoea, abdominal pain. *Biopsy:* Inflammatory cell infiltration, containing many eosinophils in caecum, large bowel, and rectum	None
Tallgren (1974)[36]	3	M	Persistent febrile upper respiratory tract infection, dry cough, dyspnoea, arthralgia, and slight knee swelling	*Postmortem examination:* Cardiomegaly, pericardial effusion, epicardial petechiae. Haematoma in right atrial wall, white miliary myocardial infiltrate. Leukaemic infiltrate and atypical eosinophils in myocardium	*Postmortem examination:* Brain swelling. Leukaemic infiltrate and atypical eosinophils in leptomeninges	Macular and petechial rash. Arthralgia, slight swelling of knees	*Postmortem examination:* Enlarged kidneys. Leukaemic infiltrate and atypical eosinophils	Dyspnoea, cough. *Chest x ray:* Miliary infiltrates. *Postmortem examination:* Lungs enlarged. Leukaemic infiltrate and atypical eosinophils	Bleeding	Hepatomegaly. *Postmortem examination:* Liver enlargement. Leukaemic infiltrate and atypical eosinophils
Thomson (1959)[47]	11	M	Sore throat, cervical lymphadenopathy, fever	Congestive heart failure, cardiomegaly, pericarditis. *Postmortem examination:* Pericardial thickening and petechiae. Heart dilated, right half hypertrophic. Right auricle enlarged with a parietal thrombus. Myocardial and endocardial fibrosis	None	Generalised oedema especially of face. Migratory polyarthritis and joint deformities	*Postmortem examination:* Enlarged kidneys	*Postmortem examination:* Oedema and blast cells infiltrate	None	Hepatomegaly. *Postmortem examination:* Blast cells infiltration
Yam (1972)[28]	12	M	Cough, diarrhoea, fever, chest pain, tingling and numbness of hands	Congestive heart failure, cardiomegaly. *Postmortem examination:* Heart dilated. Mural thrombosis and fibroblastic parietal endocarditis	Tingling and numbness of hands. Hyperreflexia, clonus, and bilateral Babinski syndrome	Petechiae. Erythematous rash. Muscle weakness	None	Cough, chest pain. *Chest x ray:* Diffuse granular infiltrate and enlarged hilar lymph node. *Postmortem examination:* Multiple infarctions and diffuse pneumonia	Diarrhoea, vomiting, nausea, abdominal pain. Perforated antral ulcer	Hepatomegaly. *Postmortem examination:* Massive liver enlargement. Heavy infiltrate of immature eosinophils and blast forms
Present case	14	F	Weight loss, anaemia, breathlessness, anorexia, lethargy, nausea, diarrhoea and vomiting, amenorrhoea, petechial rash, mouth ulcers, blisters of hands and feet, with joint and limb pain	Congestive heart failure, cardiomegaly, hypertension, systolic murmur (mitral regurgitation), pericardial effusion	None	Petechial rash, joint and limb pain	Haematuria	Cough, breathlessness. *Chest x ray:* Interstitial lung oedema, vascular redistribution, small right sided pleural effusion	Diarrhoea and vomiting	Hepatomegaly

Lymphatic/spleen	*Total white blood cell count (×10⁹/l) at presentation*	*Eosinophil count (×10⁹/l) at presentation*	*Haemoglobin (g/dl) at presentation*	*Platelets (×10⁹/l) at presentation*	*Peripheral blood white blood cell morphology*	*Bone marrow*	*Other laboratory findings*	*Duration*	*Treatment*	*Authors' diagnosis*
None	27	14 63	Not described	Not described	Vacuolated and degranulated eosinophils	Not described	Iron deficiency anaemia High serum IgG	Reported as doing well after 4 years while on Salazopyrine Diarrhoea returns within one day of stopping it	Incomplete response to prednisolone Very good response to Salazopyrine	Hypereosinophilic syndrome with isolated gastrointestinal tract involvement
Lymphadenopathy and splenomegaly *Postmortem examination* Lymph node and spleen, leukaemic infiltrate and atypical eosinophils	79	57 275	Normal	Normal	72 5% Segmented eosinophils, 2% eosinophil myelocytes and metamyelocytes	Initially Increase in myeloid cells predominantly eosinophils at various stages of maturation 'Paraleucoblasts' were seen Later Myelocytes with few 'paraleucoblasts' dominated	Mycoplasma orale type I isolated from bone marrow Cold agglutinins raised Cryoprecipitate +ve IgM G and A raised Antinuclear factor −ve Rheumatoid factor −ve, later became +ve Lupus erythematosus cell −ve	11 months	6-Mercaptopurine prednisolone methotrexate, vincristine	Eosinophilic leukaemia mycoplasma could be cause, result or fortuitous
Generalised lymphadenopathy Splenomegaly *Postmortem examination* Blast cells infiltration of lymph node and spleen	42	31 08	10 3	140	Eosinophils showed slightly basophilic cytoplasm, containing variable, mostly few coarse granules Later myeloblasts appeared in increasing numbers	Initially Increase in stem cells and cells of eosinophil series Later Myeloblasts made 43% and 'erythropoiesis completely paralysed	Reduced serum albumin Wassermann reaction and Widal's test −ve	12 months	Splenic radiation and bone radiation	Eosinophilic leukaemia
Hilar lymphadenopathy and splenomegaly *Postmortem examination* Massive splenomegaly and lymphadenopathy Heavy infiltrate of immature eosinophils and blast forms	71	51 12	12 8	Not described	Mainly mature eosinophils of different size vacuolated cytoplasm, large unevenly distributed granules decreased number of granules and mixed baso-eosinophilic granules Nuclear hypo and mainly hypersegmentation	Hypercellular Myeloid hyperplasia and eosinophilia	Coombs test −ve Lupus erythematosus cell −ve	4 months	Prednisolone, busulphan	Eosinophilic leukaemia
None	13 4	5 2	9 3	315	Eosinophils, showing partial degranulation	Hypercellular Pronounced eosinophilia	IgE, rheumatoid factor, alpha2 globulin and IgG raised Albumin low Antinuclear factor −ve Serum folate low Serum vitamin B12 high normal	After 15 months doing well	Prednisolone alternate days Eosinophils raised when prednisolone was stopped	Idiopathic hypereosinophilic syndrome

cells and basophils, peptides are released that are strongly chemotactic for eosinophils,[8 12] such as eosinophil chemotactic factor of anaphylaxis. Histamine has also been shown to be chemotactic for eosinophils. As IgE is directly involved in the triggering of mast cells with subsequent degranulation the association of eosinophilia with IgE mediated immediate hypersensitivity reaction can be explained by such chemotactic mechanisms. Eosinophil chemotactic factors that are derived from the complement system include the proteolytic fragment of C5, C5a, and the trimolecular complex $\overline{C567}$. Other recognised factors are leucotriene B4 and substances produced by some parasites.[12]

On the other hand, factors that have an eosinopenic effect on blood concentrations include corticosteroids and beta adrenergic agonists, as well as an eosinopenic factor present in inflammatory exudate, which may account for the well documented eosinopenic response that is associated with most bacterial and viral infections, apart from a few exceptions (see Table 1).[1 12]

Mechanisms of tissue damage in the idiopathic hypereosinophilic syndrome. In addition to their possible beneficial role, there is evidence that the eosinophils may occasionally be harmful to the host. For example, in asthma, it was generally held until recently that the eosinophils were protective, destroying the mast cell products that induce such clinical features of asthma as bronchoconstriction and changes in blood supply to the lungs. Several groups now feel, however, that the eosinophils may be responsible for some of the serious complications of asthma, including bronchial epithelial cell injury and even pulmonary fibrosis. It is the proteins in the distinctive cytoplasmic granules of the eosinophil that are suspected of damaging the lungs.[1]

The cytotoxic effect of eosinophil granular basic proteins on parasites has led to an examination of the potential cytotoxicity for mammalian cells.[12] Cultured intestinal, splenic, cutaneous, and peripheral blood mononuclear cells are damaged by major basic proteins. There is evidence that these enzymes play a major role in the pathogenesis of the idiopathic hypereosinophilic syndrome.[8] Of these proteins, the eosinophilic major basic protein, as well as the eosinophilic cationic protein, were found to be raised in the serum samples of patients with this syndrome.[8-11] Furthermore, degranulated eosinophils in peripheral blood smears are common in idiopathic hypereosinophilic syndrome and their presence seems to be a valuable indication of endocardial disease.[13] In vitro experiments with rat myocardial cells support the idea that components of the granules are released from the circulating eosinophil and directly damage the myocardium.[14] Eosinophilic cationic protein may also be partially responsible for the thromboembolic phenomena characteristic of this syndrome. Eosinophil granules contain potent neurotoxin, which causes demyelination and damage Perkinje cells in laboratory animals. It might be that the same, or similar, neurotoxin causes disease in patients with this syndrome.[12]

Other potential mechanisms of tissue damage include tissue infiltration with eosinophils (space occupying) and thromboembolic phenomena related to thrombi associated with endomyocardial disease.

Incidence

Idiopathic hypereosinophilic syndrome mainly affects patients between 20 and 50 years of age. The incidence is not known, but over 150 patients from different age groups have now been described. After a comprehensive search of the published reports 18 cases of this syndrome were identified in children under 16 years.[4 7 10 15-28]

Summary of the clinical details and laboratory, biopsy, and autopsy findings of the involvement of the various organ systems of the 18 children reported in these reports and the present case is shown in Table 2. Fourteen boys and five girls were affected—that is, the male predominance is less pronounced than in older age groups.

The cardiovascular system in the idiopathic hypereosinophilic syndrome

Involvement of the cardiovascular system is the main source of morbidity and mortality. Sixteen children showed evidence of this. Cardiovascular involvement in these children was generally similar to that in adult patients in its frequency and distribution.

The cardiovascular involvement in this syndrome is nearly always biventricular, but it spares the outflow tracts Characteristically, patients develop endocarditis with overlying thrombosis and, later, endomyocardial fibrosis. Involvement of the supporting structures of the atrioventricular valves often results in mitral and sometimes tricuspid regurgitation. The endocardial thrombi give rise to peripheral emboli, which further complicate the clinical picture. Patients with this syndrome are also at increased risk of developing thromboembolic disease in blood vessels of medium to large size. Disease in small blood vessels also occurs, with thickening of intimal tissue.[6]

Cases that were previously called Loeffler's eosinophilic endocarditis are probably synonymous with hypereosinophilic syndrome with severe cardiac involvement. It is now accepted that there is a range of eosinophilic heart disease, varying in severity from Loeffler's eosinophilic endocarditis, the most acute and fatal form, to Ugandan type endomyocardial fibrosis. The heart in the condition described in 1948 in West Africa by Davies, originally called endocardial fibrosis and later endomyocardial fibrosis,[29] is indistinguishable from the heart of a patient with Loeffler's fibroplastic parietal endocarditis, or eosinophilic leukaemia. Further, endomyocardial fibrosis is also known to present in non-tropical countries.

There have been reports of patients who present with an initial hypereosinophilic illness, survive, and are found at necropsy to have endomyocardial fibrosis, sometimes with features identical to Ugandan type endomyocardial fibrosis.[30] Endomyocardial fibrosis seems to be the burnt out phase of an eosinophilic heart disease.

Hearts from patients with heart failure secondary to other causes of hypereosinophilia also had necropsy appearances similar to those of patients with the idiopathic hypereosinophilic syndrome. Thus the common denominator of the cardiac lesion is probably the eosinophilia itself and not an unrecognised underlying factor.[8]

In a study of 50 patients Harley *et al* defined the non-cardiovascular characteristics that distinguish patients at risk of developing endomyocardial fibrosis from those who remained free of heart disease.[31] Patients with clinically overt heart disease were more likely ($p<0\ 05$) to be male and HLA-Bw44 positive and have splenomegaly, thrombocytopenia, raised serum vitamin B_{12} concentrations, and hypogranulated or vacuolated eosinophils and abnormal early myeloid precursors in the peripheral blood Those patients with heart disease were also more likely to have fibrosis and decreased megakaryocytes in the bone marrow. In contrast, those who remained free of heart disease tended to be female and have angio-oedema, hypergammaglobulinaemia, raised serum IgE concentration, and circulating immune complexes Appreciation of this relative degree of risk for the major complication of the idiopathic hypereosinophilic syndrome should prove useful in the early identification and appropriate treatment of patients in whom endomyocardial fibrosis might develop.

Involvement of other organs/systems

The clinical manifestation and pathological findings of the involvement of the various systems in those children who had cardiovascular involvement might have been secondary to the latter either in the form of congestive heart failure, causing, for example, pulmonary or gastrointestinal symptoms or hepatomegaly, or embolic phenomenon, originating from intracardiac thrombosis In many cases, however, the primary involvement of the various systems was also proved by biopsy or necropsy findings (Table 2)

In addition to the involvement of the cardiovascular system, which was the major problem in our present case, there are certain other features that need some emphasis.

(1) Previous history of asthma. None of the other 18 children had a similar history. Also there are a few well described adult patients who had both bronchial asthma and this syndrome.[6 10]
(2) Dramatic response to corticosteroids.
(3) Raised serum rheumatoid factor This has rarely been observed in patients with this syndrome.[9 32] Furthermore, the concentration decreased after treatment.
(4) The serum IgE concentration returned to normal after treatment. This has also been reported by Bush.[32] The changes in serum IgE concentration might be of benefit in monitoring progress, as is the eosinophil count.
(5) Low total white blood cell count at presentation, which, like initial high serum IgE concentration, has been reported to be associated with a better response to treatment
(6) In our case, her illness initially started with mouth ulcers and blisters of hands and feet. This combination has not been reported before. Presentation of the idiopathic hypereosinophilic syndrome with mouth ulcers has been reported in two patients, who were 26 and 51 years old.[33] In these patients, however, there was ulceration of other mucous membranes, including the genitalia.

Treatment

The idiopathic hypereosinophilic syndrome is a rare disorder, but one that is accompanied by high morbidity and mortality Recent vigorous treatment regimens, however, directed at lowering the eosinophil count with symptomatic treatment of complications of the organ systems, has brought about a tremendous improvement in survival and prognosis. The mainstay of treatment is corticosteroids. Hydroxyurea is used in patients who do not respond or only partially respond to steroids.[34] Its use may also be required to allow the steroid dosages to be reduced in patients who require maintenance treatment. Vincristine has also been used recently in a number of patients with aggressive disease. Anticoagulants are required in most patients.[10] Drugs that inhibit platelet function—for example, dipyridamole, have also been used. Leucophoresis and plasma exchange do not seem to have any clinical benefit, unless the patient also had increased whole blood viscosity and widespread vessel occlusions.

Patients without dysfunction of organ systems are not treated and are followed closely at three to six monthly intervals.[34] If patients show dysfunction of organ systems they are treated initially with corticosteroids. If the disease stabilises or improves the steroid is continued on an alternate day regimen Ultimately, it is tapered to the lowest possible dose that will control that disease. If the disease progresses despite steroids a cytotoxic agent, specifically hydroxyurea, is added with the aim of maintaining the leucocyte count at less than $10\times10^9/l$ with a normal eosinophil count.

Prognosis

Favourable prognostic factors that indicate better response to treatment are high serum IgE concentration, the presence of angioneurotic oedema, and unmistakable eosinopenia within a few hours after the first dose of prednisolone Unfavourable prognostic signs are pronounced leucocytosis and myeloblasts in peripheral blood and congestive heart failure.[4 34] It is also important to look for the possibility of high serum vitamin B_{12} and low serum folate concentrations, abnormal leucocyte alkaline phosphatase activity, chromosomal abnormalities, and basophilia of more than 3%. These leukaemic markers as a group seem to have a predictive value in terms of symptomatology and response to treatment. Those with positive findings had more severe disease.[4]

Eosinophilic leukaemia

Many patients of various age groups with this syndrome, including eight children in our review, were reported as having eosinophilic leukaemia. Although this is one extreme of this syndrome, most patients do not seem to have leukaemia. Rickles and Miller suggested the following criteria for a diagnosis of eosinophilic leukaemia.[35]

1. (1) Pronounced and persistent eosinophilia, associated with immature forms, either in the peripheral blood or bone marrow
2. (2) Greater than 5% blast forms in the bone marrow.
3. (3) Tissue infiltration by immature cells of predominantly eosinophilic type.
4. (4) An acute natural history measured in months, accompanied by anaemia, thrombocytopenia, increased susceptibility to infection, and/or haemorrhage.

Although the hypereosinophilic syndrome was originally defined in the context of primary eosinophilia, it is now recognised that the same involvement of organ systems may arise when eosinophilia occurs secondary to a defined condition—for example drug reactions and parasitic disease[1 2 4] —so that early identification and prompt treatment of the primary condition, which usually results in the disappearance of the hypereosinophilia, may prevent these complications

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Short reports

Recovery from neonatal myocardial dysfunction after treatment of acute hypertension

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SUMMARY Echocardiography showed gross cardiac dysfunction in a neonate with hypertension secondary to renal artery thrombosis. Cardiac recovery was dramatic after control of hypertension with captopril.

Case report

A 2580 g girl was born at 37 weeks' gestation by repeat caesarean section to a 33 year gravida 2, para 1 mother. Apgar scores were seven and nine at one and five minutes. The baby developed progressive respiratory distress that required insertion of an umbilical artery catheter through which fluids and medications were administered. Her course was complicated by a right sided pneumothorax and finally the need for assisted ventilation at 68 hours of life after which she was referred to our neonatal intensive care unit

On admission she had a pulse rate of 126 beats/min and central blood pressure of 86/62. On assisted ventilation, she had good air entry with normal heart sounds and no murmur or gallop. She had no oedema. Liver edge was 2 cm below the right costal margin. The right kidney was palpable Blood count and serum electrolyte concentrations were normal. Serum creatinine concentration was 109 μmol/l Urinalysis showed proteinuria, haemoglobinuria, and red blood cells. Chest radiograph showed cardiomegaly and pulmonary vascular congestion with the catheter tip at the ninth thoracic vertebra. A renal ultrasound scan initially yielded normal results.

Over the next 48 hours, her systolic blood pressure increased from 85 to 120 mm Hg. She developed increasing heart failure with liver enlargement up to 5 cm below the right costal margin, poor perfusion, and falling urine output Electrocardiography showed ST and T wave changes consistent with ischaemia Echocardiography at 6 days of age showed left atrial and left ventricular enlargement but no structural abnormality. Left ventricular shortening fraction was only 10%. Cardiac catheterisation confirmed poor left ventricular function with generalised hypokenesis of the left ventricle. The origin of the left coronary artery was normal. On repeat ultrasound scanning the right kidney, although of normal size, showed increased echogenicity with loss of corticomedullary differentiation and normal pyramid architecture. The right kidney was not seen on ^{99m}tc-glucoheptonate scan. An aortogram showed thrombosis of the right renal artery.

The umbilical artery catheter line was then removed and the baby heparinised. Infusion of digoxin, furosemide, hydralazine, and even nitroprusside up to 3 μg/kg/min did not affect her blood pressure or clinical condition. Response to diazoxide was transient. Her systolic blood pressure was finally controlled below 80 mm Hg with oral captopril 1 mg every eight hours, with dramatic resolution of heart failure and improved clinical condition within hours.

Repeat echocardiography (30 hours after the first echocardiogram had been taken and 24 hours after the blood pressure had been controlled) showed complete recovery of left ventricular function. Left atrial and ventricular dimensions were normal. Left ventricular shortening fraction was 37%.

Serum creatinine concentration peaked at 136 μmol/l, accompanied by mild hyponatraemia (serum sodium concentration 132 mmol/l) before control of blood pressure. Both gradually returned to normal.

Captopril was given for eight days with excellent control of blood pressure, which remained normal after treatment had been stopped The baby thrived and was discharged at 17 days. Follow up at 2 months revealed a normotensive child with normal biochemical profile and no evidence of heart failure.

A renal scan continued to show a non-functional right kidney.

Discussion

Renal artery thrombosis with renin induced hypertension is a recognised complication of umbilical artery catheterisation.[1] Although renin concentrations were not measured, confirmed renal artery thrombosis with failure to respond to other antihypertensives and prompt response to captopril make renin mediated hypertension most likely.

Hypertension in neonates has been described as blood pressure greater than 90/60 mm Hg in term infants and 80/45 mm Hg in premature infants.[1] Cardiorespiratory symptoms and congestive heart failure are the most common symptoms of neonatal hypertension.[2] The degree of hypertension necessary to produce congestive heart failure may vary with individual neonates. The maximum pressure of 123/81 recorded in our patient was moderate A very limited myocardial contractile reserve in response to increased afterload has been shown in newborn lambs.[3 4] Inotropes have limited effects on contractility in newborn rabbits and lambs.[5 6] Limited myocardial reserve may explain why congestive heart failure is often the dominating picture in neonatal hypertension.

Hypersensitivity to captopril, manifesting in some adults as hypotensive crisis, has not been reported in neonates.[7]

We have shown by echocardiography that adequate treatment of hypertension rapidly reverses severe myocardial dysfunction caused by neonatal hypertension. We suggest that echocardiography may be helpful to document the cardiac effects of neonatal hypertension and to determine the need for and response to treatment

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Anticonvulsant drugs, growth, and development

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SUMMARY Height and stage of puberty of 67 children with epilepsy were measured before beginning treatment with anticonvulsant drugs and annually to a maximum five years' treatment. Blood concentrations of the drugs used (phenytoin, sodium valproate, carbamazepine, ethosuximide, and phenobarbitone) were monitored throughout. No significant deviation in growth patterns was detected.

Anticonvulsant drugs administered during pregnancy have been postulated to retard fetal growth[1] and head circumference.[2] In vitro studies have shown that phenytoin and sodium valproate reduce the thickness and cellularity of epiphyseal and articular cartilage in rats.[3] Round described a group of children with chronic epilepsy who failed to reach predicted adult height and attributed this to an early growth spurt and lower than normal growth velocity [4] Robinson found premature epiphyseal fusion in a group of short children with epilepsy treated medically [5]

In a study of adults with epilepsy McGowan identified three groups who seemed to be short: (1) males with partial seizures beginning before 18 years of age, (2) females who had taken phenytoin before the onset of puberty, and [illegible] males who were on phenytoin before 10 years.[6] Interpretation of these studies is difficult, however, as many of the patients had chronic epilepsy treated with anticonvulsant polytherapy, without access to monitoring of drug concentrations, and many of these children were educated in a residential setting. We have therefore prospectively investigated growth in a group of children with newly diagnosed epilepsy from the beginning of treatment.

Patients and methods

The 67 children included in our study were already participating in a large comparative monotherapy study of children with newly diagnosed epilepsy who had had regular measurements of anticonvulsant concentrations. Of the 67, 34 were boys (mean age 7·9 years, range 3·1–15·2 years) and 33 girls (mean age 10·9 years, range 4·0–15·0 years) and 58 were white and nine Afro-Caribbean. The average duration of follow up was 3·1 years (range 0·9–5·4 years). Thirty three children had primary generalised epilepsy and 34 had partial seizures. Children were treated in accordance with the study protocol. Treatment began with a single drug in a fairly low dose calculated according to body weight, with subsequent increases until control of seizures was obtained or the anticonvulsant concentration reached the upper limit of the defined therapeutic range (Table 1). Children who failed to achieve control of seizures on treatment with a single drug were placed on polytherapy.

A standardised measure of height by two observers (EM and MM) and pubertal staging was recorded before treatment was begun (initial) and then at annual intervals, the most recent measurements have been taken as the end point for analysis (final).

Height data are presented in terms of standard deviation score (SDS), using known population measurements. This gives an indication of the stature of the subject relative to a normal population of that age, a value of 0 being average and + and − values representing degrees of tallness and shortness, respectively.

Skeletal maturity in 31 children (13 girls and 18 boys) was determined by one of us (CM) from radiographs of the left hand and wrist before treatment was begun and in 20 children at 12 months, 16 at 24 months, 11 at 36 months, seven at 48 months, and three at 60 months.

Statistical analysis of the height SDS at initial and final measurement was by comparison of mean values and 95% confidence intervals. Results are expressed as mean (SD).

Results

Height SDS. The height SDS for boys and girls at the initial and final examinations are shown in Table 2. There was no significant difference in these measurements compared with those of the normal population. The mean difference between initial and final height SDS for boys was 0·04 (95% confidence limits −0·12 to 0·19, t=0·47, df=33, p=0·64) and for girls was −0·07 (95% confidence limits −0·29 to 0·15, t=0·643, df=32, p=0·52).

Table 2 *Height standard deviation scores (SDS) for boys and girls with epilepsy treated with anticonvulsant drugs at initial and final examinations Values are mean (SD)*

Height SDS	*Boys*	*Girls*
At initial examination	0 02 (1 1)	−0 03 (1 1)
At final examination	0 06 (1 2)	−0 10 (0 9)
Δ	0 04 (0 44)	−0 07 (0 6)

Table 1 *Treatment protocol for administration of anticonvulsant drugs to children with epilepsy*

Drugs given	*No of patients*	*Drug dosage (mg/kg)*		*Drug concentration (mg/ml)*		
		Initial	*Increment*	*Mean during treatment*	*Range*	*Therapeutic range*
Carbamazepine (CMZ)	21	8	4	5 8	1 4–18 3	4–10
Phenytoin (DPH)	19	5	2	7 1	2 0–38	10–20
Sodium Valproate (SV)	9	15	5	53	3 6–144	50–100
Ethosuximide (ESM)	3	15	5	32	25 3–28 5	50–100
Phenobarbitone (PB)	3	3	2	13 4	12 8–18 6	20–40
Patients on polytherapy	12					
SV+CMZ	6					
SV+CMZ+DPH	1					
SV+ESM	3					
SV+ESM+CMZ	1					
CMZ+DPH+Clobazam	1					

Sexual maturity.

Girls

Of the 33 girls, seven had their menarche before starting medication (mean age 12·0 years, range 9·9–14·1 years), 11 girls were prepubertal, and the remaining 15 had their menarche while on treatment (mean age 13·4 years, range 11·3–15·3 years) The normal mean age for menstruation is 13·0 years. The pubertal ratings as determined at the last visit did not deviate from the normal pattern

Boys

In the group of 34 boys, four were in puberty before starting treatment, 14 were prepubertal, 16 entered puberty while on treatment (mean age for penis stage II 11·3 years, range 8·5–14·3 years; mean for population 12·0 years; and mean age for pubic hair stage II 13·1 years, range 11·3–14·2 years; mean for population 12·5 years).

Skeletal maturity

There was a trend for girls to show slightly earlier skeletal maturity than is normal, although the maturity scores were still within normal limits. The skeletal maturity in boys was normal

Discussion

These results show that children with epilepsy on anticonvulsant drugs for a mean of three years (range 0·9–5·4 years) grow and mature normally. We found no significant difference from the normal timing of the menarche or of onset of puberty. There was a trend towards earlier skeletal maturity in the girls, but this did not influence final height. Separate examination of children with partial seizures, those taking monotherapy, children with persistent seizures, and a small number on polytherapy, again produced no evidence of deviant growth patterns.

Some of the previously reported findings[4–6] were possibly related to adverse enviromental factors, high seizure frequency, or subclinical drug toxicity.

We thank Dr E H Reynolds and Dr B Neville for allowing us to study their patients

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Age distribution of anginose mononucleosis

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SUMMARY The age distribution of anginose infectious mononucleosis in children was analysed retrospectively for the years 1966–85. During that period the disease became significantly more common in children of a young age and less common in older children. This shift could not be attributed either to socioeconomic conditions or to the diagnostic methods used.

The clinical and epidemiological range of infectious mononucleosis (IMN) has been appreciated only in the past decade, since the introduction of specific serological tests. Infection during infancy and childhood is usually subclinical,[1] whereas the classical clinical manifestations are common among adolescents and young adults. It has been reported that infection generally occurs at an earlier age in low socioeconomic groups, where overcrowding and poor hygiene prevail.

One of the clinical presentations of IMN is the anginose type.[2] Although this is said to be more prevalent in older children and adolescents, we have gained the impression that it is also common in younger children. We therefore studied retrospectively the age distribution of anginose mononucleosis in our paediatric population over the past 20 years.

Patients and methods

Hospital records of all children diagnosed with glandular fever, IMN, suspected IMN, or the mononucleosis syndrome in the department of paediatrics, Tel-Aviv Medical Center from 1966 to 1985 were searched. Cases of the anginose type of IMN were selected for further analysis according to eight criteria. (1) Temperature of greater than 38°C for 72 hours or more; (2) exudative tonsillitis present for at least 72 hours that had not responded to treatment with penicillin for at least 48 hours; (3) cervical lymphadenopathy; (4) blood smear containing more than 10% atypical lymphocytes; (5) raised liver enzyme (serum aspartate transaminase and alanine transaminase) activities; (6) positive results to serological tests (from 1966 to 1974 the Paul-Bunnell test, from 1975 to 1979 the Monospot slide test or Paul-Bunnell test, and from 1980 to 1985 specific tests for Epstein-Barr virus (virus capsid antigen IgG and IgM)); (7) negative results to serological testing for cytomegalovirus (from 1970); (8) negative results to serological testing for toxoplasma (from 1966 to 1977 a dye test and from 1978 on a fluorescence test).

Patients fulfilling all eight criteria were diagnosed as definitely having anginose IMN. As heterophilic antibody tests may yield negative results in up to 60% of patients younger than 6 years old[3] we included in our study all patients who were negative for heterophilic antibody during 1966–79 (before specific tests for Epstein-Barr virus were performed) but who fulfilled all other criteria. All the patients included in the study during 1980–5 were positive for Epstein-Barr virus.

The significance of differences in age distribution of anginose IMN in the different periods studied were analysed with the χ^2 test.

Results

The number of patients diagnosed as suffering from anginose IMN from 1966 to 1985 was 1290. The ratio of female:male patients aged under 5 years was 1:2·4 and aged 5–18 years 1:1·9 (in adults during the past five years it was 1:1·6). The Table shows the distribution of cases according to age groups and calendar years. The ratio of patients aged 10 and over to those aged under 10 was 12·25:1 during 1966–70, 5·93:1 during 1971–5, 1·83:1 during 1976–80, and 0·83:1 during 1981–5.

Table *Age of patients, time of diagnosis, and numbers positive for Epstein-Barr virus*

Time of diagnosis		*Age (years)*				
		<5	*5–9*	*10–14*	*15–18*	*Total No*
1966–70	No (%) of cases	3(1)	17(6)	52(20)	193(73)	265
	No seropositive	0	9	43	125	177
1971–5	No (%) of cases	14(4)	31(10)	103(33)	164(53)	312
	No seropositive	5	20	89	134	248
1976–80	No (%) of cases	42(12)*	79(23)	161(47)	61(18)*	343
	No seropositive	28	52	112	59	251
1981–5	No (%) of cases	90(24)*	112(30)	98(26)	70(19)*	370
	No seropositive	90	112	98	70	370

*$p<0·05$ compared with 1971–5 and 1966–70

Discussion

Clinically apparent IMN, including the anginose form, is most common in developed, industrialised countries and among high socioeconomic groups, in which exposure to Epstein-Barr virus occurs in the second decade of life.[4] Most cases are diagnosed when the patients are over the age of 10, with a peak incidence in the 15–25 age group. In developing countries, tropical areas, and low socioeconomic groups exposure to Epstein-Barr virus occurs in early childhood and infections are predominantly asymptomatic or associated with mild, non-specific manifestations.[5] Thus in both developed and developing countries and among all socioeconomic classes clinical IMN is uncommon in early childhood.

Whereas this age distribution was true for anginose IMN in our community 20 years ago, during the past decade this form of the disease has shifted noticeably towards a younger age group. About one quarter of the cases now occur in children under 5 years old, and more than half occur in those younger than 10. This is in great contrast to the distubution 20 years ago, when more than 90% of cases occurred in children over the age of 10. Moreover, our data also show a decline in anginose IMN during adolescence.

Although we are fully aware of the potential flaws of a retrospective study, and despite the differences among serological tests used in the different periods studied, we believe that our diagnostic criteria were strict enough to establish adequately the diagnosis of anginose IMN and preclude such conditions as infection with cytomegalovirus, toxoplasmosis, streptococcal pharyngitis, infectious hepatitis, and adenovirus pharyngotonsillitis (the main differential diagnoses).

The shift in age distribution of anginose IMN in our community cannot be attributed to socioeconomic conditions as these have been constantly improving in our urban community over the past 20 years, nor can it be related to the emergence of new diagnostic tests because the changing pattern was observed before such tests were available in our medical centre.

Interestingly, Sumaya *et al* prospectively evaluated children with documented IMD induced by Epstein-Barr virus between 1976 and 1982[6] and concluded that 'an unexpected finding was the large number of young children less than 4 years old with this disease.' They found that 45% of their patients under 4 years old had exudative tonsillopharyngitis. They also found, as we did, that the incidence in boys was more than twice that in girls. The similarity of their data, from the United States, to ours implies that the increase in the occurrence of clinical IMN in early childhood may be a worldwide rather than a local phenomenon.

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Referral to a regional centre improves outcome in extremely low birthweight infants

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SUMMARY Referral of extremely low birthweight infants (< 1001 g) from district hospitals in a geographically defined area to a specialist regional centre significantly improved their chances of survival.

Referral of preterm infants or of their mothers antenatally to a regional unit has been widely accepted as improving outcome, though there is little evidence to support this belief. Reports of improved survival either compare results before and after the introduction of a transfer programme, with the problem of historical controls, or contrast the outcome of infants transferred to a regional unit with that of those left behind, though such groups are not comparable.[1] This study compares the 28 day mortality of extremely low birthweight infants in eight geographically defined areas with the rate of referral from their district hospitals to a regional perinatal centre.

Methods

Mersey regional neonatal intensive care unit is in Liverpool Maternity Hospital and with the obstetric units provides a regional perinatal referral service for Mersey region and north Wales For the purpose of this study I divided the region into eight areas corresponding to district or area health authorities. These areas were Clwyd, Gwynedd, West Cheshire, (Chester, Warrington, Halton), East Cheshire (Crewe and Macclesfield), St Helens, Liverpool, Sefton (North and South), and Wirral.

The data for the study were obtained from forms LHS 27/1 for each district for the years 1980–3 inclusive and the admissions records of the regional neonatal intensive care unit. Form LHS 27/1 is completed by each district health authority yearly and returned to the regional health authority and to the statistics department of the Department of Health and Social Security in Blackpool or, in the case of Wales, the Welsh Office in Cardiff. Information reported on the form includes the number of

Table *Referral rates of extremely low birthweight [ELBW] infants from different health districts in relation to their birth rates and mortality of low birthweight [LBW] and ELBW infants*

Area	*Corrected mortality of of LBW infants*	*Corrected rate of LBW infants*	*Mortality of ELBW infants*	*Rate of ELBW infants*	*Referral of ELBW infants (%)*
West Cheshire	18	53	375	1·87	83
East Cheshire	5	69	862	2·92	0
Clwyd	8	58	681	2·40	38
Gwynedd	17	56	600	1·81	65
St Helens	15	72	696	3·73	38
Sefton	28	60	741	1·92	4
Wirral	27	60	525	2·61	56
Liverpool	39	70	513	3·38	99

notifications of births to mothers normally resident in the district concerned adjusted by any notifications of births to mothers transferred in or out of the area, together with the place of birth. Births are also recorded on the form in birthweight groups for infants of 2500 g or less, with the age of death of those dying in the first month notified as day 0, 1–7 days, and 7–28 days. The records of the regional intensive care unit yielded the number of extremely low birthweight infants admitted and the mothers' place of residence. Both in utero and postnatal transfers were included.

From these data I derived the following variables for each area: corrected rate of low birthweight (1001–2500 g) infants per 1000 live births, corrected neonatal mortality of low birthweight infants per 1000 live births, rate of extremely low birthweight infants per 1000 live births, neonatal mortality of extremely low birthweight infants per 1000, referral rate of extremely low birthweight infants to the regional centre, and distance of the principal district hospital in each area from the regional centre. The Table shows these figures for each of the eight areas. Correlations between variables for the areas were sought with Spearman's rank correlation test.

Results

Altogether 201 extremely low birthweight infants were referred over the four years, and the referral rate varied between 0% and 99%. Mortality at 28 days ranged from 375 to 862/1000. A significant correlation between referral rate and lower mortality was observed ($r=0·92$ $p<0·01$). The 28 day mortality for extremely low birthweight infants would obviously be affected by the number of infants registered as liveborn in a given area; this varied between 1·8 and 3·7/1000. It has been suspected that some hospitals do not register very small infants who are likely to die, particularly when intensive care is not readily available. To investigate this possibility the rate of extremely low birthweight infants was compared with the corrected rate of low birthweight infants for each area there was a strong correlation between the two ($r=0·96$, $p<0·01$).

There was no significant correlation between the rate of low birthweight infants and mortality of these infants or between the rate of extremely low birthweight infants and mortality in the eight areas. The distance in miles of the main hospital in each area from Liverpool did not correlate with referral rate.

Discussion

Advances in neonatal intensive care have undoubtedly contributed to improvements in the survival of extremely low birthweight infants. Crude comparisons between the populations treated in referral centres and district hospitals have, however, suggested that such gains are minimal and that little benefit exists in referring very tiny infants.[2] In this study I looked at the effect of transfer on the smallest infants, among whom any effect would be most obvious. Each area had the same opportunity to refer infants, and during the time of the study the regional unit was rarely unable to accept any referral. The rate of referral did not correlate with the distance from the regional unit but presumably depended on the policy of the individual district hospitals. Failure to register extremely low birthweight infants as live births would have a serious effect on a study such as this. The wide variation in rates of extremely low birthweight infants (1·8–3·4/1000) might indicate that this was happening The rate for each area, however, correlated well with the corrected rate of low birthweight infants, suggesting that non-registration of these infants was unlikely and that the variation in rates was real reflecting socioeconomic conditions rather than attitudes to resuscitation at birth. The neonatal mortality in both extremely low birthweight and low birthweight babies did not correlate significantly with their respective rates of occurrence, suggesting that even in areas of socioeconomic deprivation with high rates of low birthweight babies outcome may be independent of this. Extremely low birthweight infants form a high risk population but represent only about 4:1000 of all infants born. Though this study shows that such tiny infants do best when referred to a regional centre, the effect of referral may not be as pronounced in larger infants, and further studies are necessary to clarify the issue.

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Blood cultures in neonates with percutaneous central venous catheters

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SUMMARY We compared the results of 74 pairs of blood cultures obtained simultaneously every two weeks from a peripheral vein and a percutaneously inserted central venous catheter in 38 newborns. Three babies (7·9%) had bacteraemia. In two of these the central catheter was colonised 48 hours beforehand.

In most of the reported cases of sepsis related to the use of central venous catheters the diagnosis was based on the natural history or on a positive result of a blood culture obtained either from a peripheral vein or through the catheter. We considered that by obtaining simultaneous blood cultures from a peripheral vein and the catheter, it might be possible to identify catheter colonisation before peripherally drawn blood samples yielded a positive culture.

Patients and methods

Thirty eight neonates, including 27 who weighed less than 1·25 kg, with percutaneously inserted silastic central venous catheters were studied. Clinical data are summarised in Table 1. Catheters were inserted using the peripheral veins of the extremities and scalp exclusively.[1] The infusion included FreAmine III (American McGaw, American Hospital Supply Corporation) and 10% Intralipid (Cutter Laboratories). All infusions and adminstration sets were changed daily by the nurses under sterile conditions.

Table 1 *Clinical characteristics of the 38 infants studied Values are mean (SD) [range]*

Birth weight (g)	1228	(705)	[620–2930]
Gestational age (weeks)	29·2	(4·4)	[25–42]
Postnatal age (days)	19·6	(15·7)	[1–81]
Weight when catheter put in place (g)	1515	(790)	[650–3320]

The 1 ml blood samples were drawn simultaneously, one from a peripheral vein and the other through the central catheter, at two weekly intervals for as long as the catheters were in place. Each blood specimen was cultured on aerobic and anaerobic culture media. Aerobic culture medium consisted of 10 ml tryptic soy agar broth and the anaerobic culture medium of 10 ml brain heart infusion broth. Blood cultures were inspected daily for seven days

Results

The mean (SD) duration that catheters were in place was 34·5 (20·6) days, with a range of 14–95 days. Seventy four sets of blood cultures were obtained routinely. In addition, eight sets of blood cultures were drawn because of clinical suspicion of infection, but all yielded negative results Results of the routine cultures are shown in Table 2. Three of the 38 patients had positive blood cultures, an incidence of bacteraemia of 7·9%. These three cases are described in more detail below. In the first two patients the catheter was colonised before a positive culture was obtained from peripheral blood.

Case 1. A patient with a birth weight of 2880 g was receiving assisted ventilation for the management of

Table 2 *Results of routine peripheral and central line blood cultures (n=74) drawn from the 38 patients*

	Catheter duration at time of blood cultures (days)					
	14	*28*	*42*	*56*	*70*	*84*
No of paired blood samples cultured	38	19	11	3	2	1
No of positive blood cultures						
Peripheral vein	1	0	0	0	0	0
Percutaneous central venous catheter	1	2*	0	0	0	0

*Peripheral vein blood cultures became positive 48 hours later

omphalocele, ventricular septal defect and overriding aorta. Blood culture drawn through the catheter four weeks after the catheter had been put in position was positive for group D enterococcus, while the simultaneous blood culture from a peripheral vein yielded negative results A repeat blood culture from the peripheral vein 48 hours later was positive for the same organism.

Case 2. An infant with a gestational age of 27 weeks and birth weight of 800 g was receiving assisted ventilation for respiratory distress syndrome. Blood culture drawn through the catheter at four weeks was positive for non-haemolytic streptococcus. Simultaneous blood culture from the peripheral vein yielded negative results. Repeat blood cultures performed through the catheter and a peripheral vein 48 hours later were both positive for non-haemolytic streptococcus.

Both patients were treated successfully after elective catheter removal.

Case 3. This infant, who had a gestational age of 26 weeks and a birth weight of 670 g, was on assisted ventilation for chronic lung disease. Blood cultures drawn simultaneously through the catheter and a peripheral vein at the end of two weeks were both positive for *Staphylococcus epidermidis*. As this infant was clinically stable we elected to treat him with antibiotics, without removal of the catheter. Subsequent blood cultures taken through the catheter and a peripheral vein 48 hours after treatment was begun yielded negative results No further episodes of infection occurred in this patient.

Discussion

Sepsis remains the most important complication related to the use of central venous catheters. Infection rates of 6–20% have been reported in older patients,[2] higher rates have been reported in newborn infants.[3 4] To our knowledge, this is the first prospective evaluation of the use of simultaneous blood cultures, obtained from a peripheral vein and through a central catheter, during infection surveillance in sick neonates receiving parenteral alimentation through percutaneous central venous catheters. In our population we found a low incidence of bacteraemia (7·9%). This compares favourably with previous reports in neonates and young infants receiving parenteral nutrition through surgically placed Broviac catheters (26·6% and 31·6%, respectively).[3 4]

Polymicrobial bacteraemia associated with the use of lipid emulsions in a neonatal intensive care unit had been reported by Jarvis and coworkers.[5] Powell *et al* isolated *Malassezia furfur* from blood cultures drawn from Broviac catheters in five infants receiving fat emulsions through the central lines.[6] They postulated that contamination of the catheter at the time of placement might be the most likely origin of infection. Despite the simultaneous use of FreAmine III and Intralipid, the incidence of bacteraemia in our study did not differ from that reported by Loeff *et al* in neonates and young infants receiving parenteral nutrition, exclusive of fat emulsions, through small silastic catheters.[3] Thus the addition of Intralipid did not influence the infection rate in our study.

A positive blood culture obtained through a central line, in the face of a simultaneous negative peripheral venous blood culture, suggests catheter colonisation. This group of infants will benefit from removal of the central venous catheters. If we had relied solely on the blood cultures from the peripheral veins we would have missed the catheter colonisation in two of our patients. Positive blood cultures obtained through the catheters enabled us to identify the onset of infection early and helped us in the management of these patients.

Our findings suggest that the use of percutaneously inserted small central venous catheters is associated with a low incidence of bacteraemia in sick neonates receiving parenteral alimentation and that in addition to peripheral venous blood cultures, percutaneous central venous catheters can be used to obtain blood cultures for the early detection of catheter colonisation in newborn infants

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Congenital hypertrichosis lanuginosa: neonatal shaving

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SUMMARY A newborn baby presented with overgrowth of lanugo hair and a precocious tooth. She was shaved infrequently until aged 9 months, when spontaneous loss of body hair began. Pyloric stenosis at 6 weeks was surgically corrected. There was a family history of hypertrichosis and dental anomalies.

Congenital hypertrichosis lanuginosa is a rare disorder that causes persistent, excessive lanugo and dental anomalies. Neonatal and determatological textbooks do not provide guidance on immediate management: this report describes one approach, shaving.

Case report

The baby girl, the first child of unrelated parents,

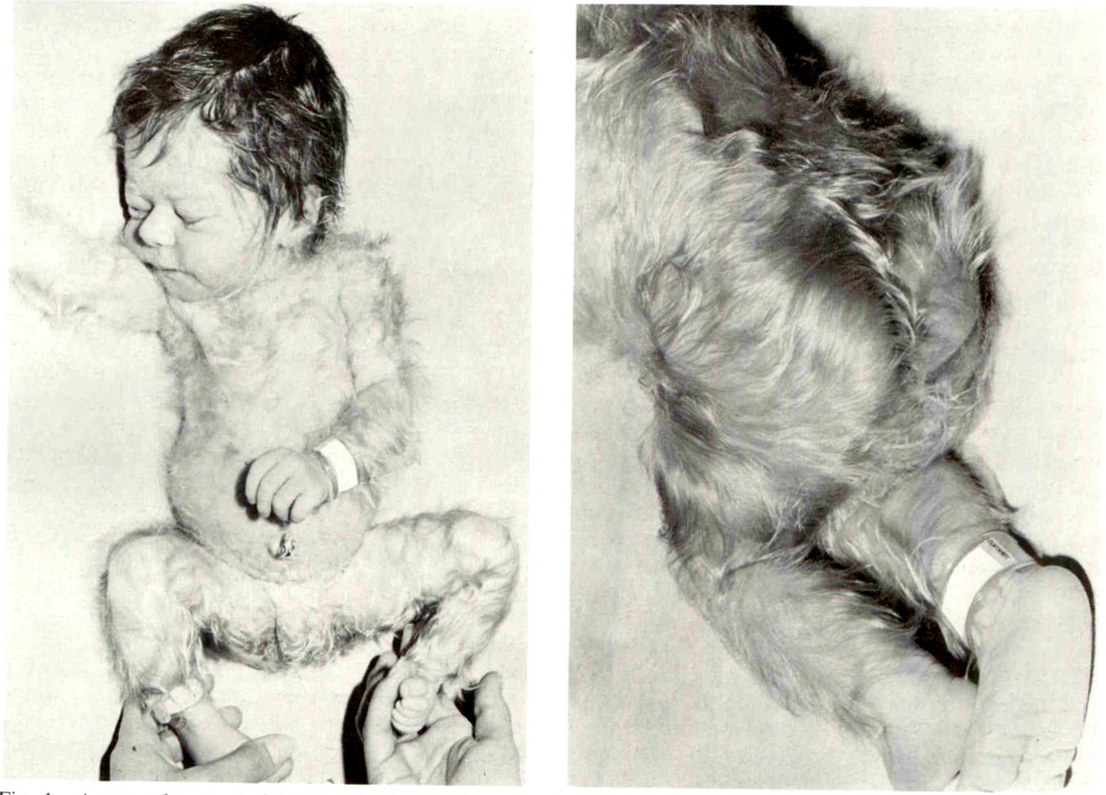

Fig. 1 *A case of congenital hypertrichosis lanuginosa at presentation at 4 days of age.*

was covered at birth with long, curly blond hair, which spared only her hands, feet, and face (Fig. 1). It was soft and silky, up to 2·5 cm long, encroached onto the forehead, cheeks, pinnae, and inside the external auditory meati, and extended to the margins of the labia minora and anal verge. The scalp hair was the same length and texture, but darker and thicker. There was a partially erupted upper central incisor tooth but no other abnormality: she weighed 3350 g, with length 49·5 cm and head circumference 35 cm.

The mother, a hairdresser, denied using any hair promoting applications at work. The father, an airforce technician, admitted that members of his family were, or had been, excessively hairy. He himself had been very hairy at birth, with a precocious tooth. His excess hair had gradually disappeared, though he had needed dentistry for supernumerary secondary teeth. Affected members of his family were all born with a single tooth. There was sparse but unusually long hair on his forearms and the dorsal surface of his hands: his hair distribution elsewhere was normal.

Dermatology textbooks provided the diagnosis but no help with immediate management, and the parents wanted 'something to be done'. Mother and baby were nursed in a single room, for privacy, but she did not express any feelings of alienation about her daughter, whose thick curls were not unattractive. Indeed, when she went to a routine demonstration of baby bathing for new mothers, she returned disconcerted: 'that baby was *completely bald*'.

Embarrassment, and the difficulty in keeping the profusely hairy nappy area clean, persuaded the parents and myself that shaving was necessary. We used a conventional razor on the fourth day, but after an hour, and with only half the baby shaved, this method was abandoned. The following day an electric 'Ladyshave' razor, used dry, completed the shave in half an hour, easily and painlessly. They went home the same day: the baby was breast fed.

She was admitted aged 5 weeks with pyloric stenosis, which was treated successfully by pyloromyotomy. There was no family history of this. She was shaved all over every two weeks or so until 3 months of age, when arms and legs only were shaved, monthly. Her mother stopped shaving her by 9 months, when body hair was spontaneously being shed. At 14 months there was only excess hair around her ears, wrists, buttocks, and ankles (Fig. 2). Her eyelashes were very long, and her scalp hair needed cutting four times in the first year. When last seen, at the age of 19 months, she was having trimmings to the facial and aural hair every three to four months.

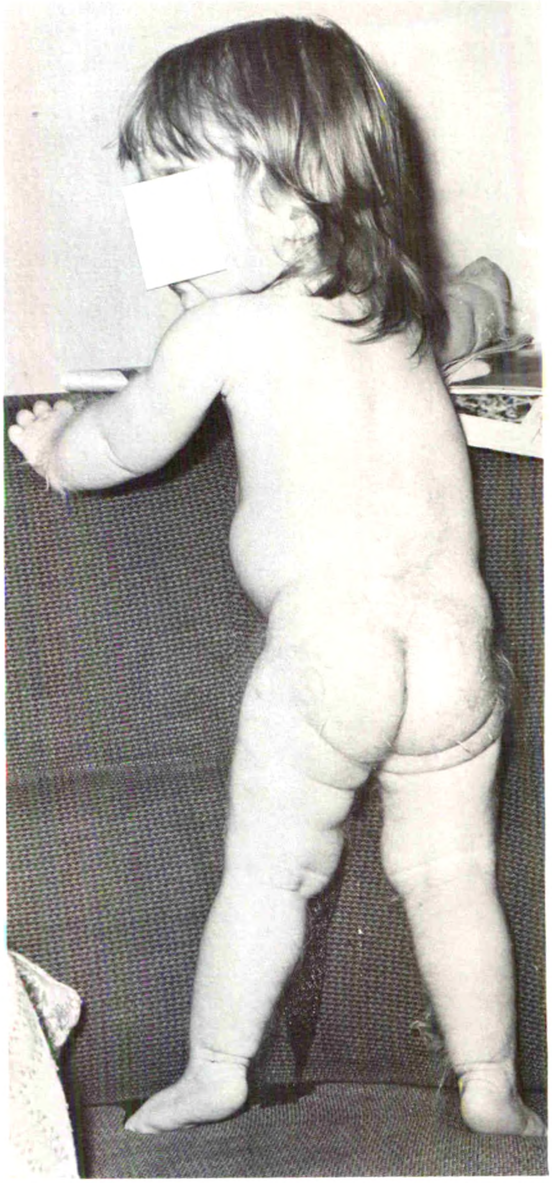

Fig. 2 *The case at 14 months of age, after no shaving for five months, showing spontaneous hair loss.*

The precocious upper incisor was shed in the first week. Two lower incisors appeared at 9 months, four more by 14 months, with a gap at the position of the neonatal tooth, where a tooth finally erupted at 17 months. The primary incisors appeared unusually small (Mr D R Purnell, Consultant Oral Surgeon).

Discussion

Excess hair in childhood may be due to either *hirsutism*—that is, androgen induced, with an adult sexual distribution of coarse 'terminal' hair (for example, the adrenogenital syndrome)—or *hypertrichosis*—that is, an excess of vellus or lanugo hair, drug induced (for example, phenytoin or diazoxide) or accompanying a syndrome (for example, de Lange's or Hurler's syndromes)

Congenital hypertrichosis lanuginosa is almost invariably transmitted as an autosomal dominant with varying expressivity.[1 2] In some families the hairiness is present at birth and persists and in some it diminishes; other case reports describe little excess hair at birth, but increasing hair growth into adult life. Anomalous dental eruption is common and sometimes there are ear malformations: pyloric stenosis is not reported.[1 3]

Management includes dental care, counselling, shaving, bleaching the hair, and chemical and electrical epilation. A 4 year old boy's hypertrichosis was controlled by shaving and epilatory creams, but at birth only his facial hair was excessive, and generalised hypertrichosis developed during infancy and diminished in later childhood.[2] No treatment is mentioned of two children aged 3 and 16 months whose similarly affected mother shaved and used chemical and electrical epilation, and neonatal shaving is not described in the accompanying review of other case reports.[3] It is reassuring that shaving does not increase the profusion or rate of regrowth of hair,[1 4] despite what old wives' tales may warn, or young shavers hope, to the contrary.

Congenital hypertrichosis lanuginosa is a very rare condition, with about 40 case reports.[1] Beighton quotes an incidence of one in 1000 million [2] When presented with a newborn baby affected by a rare syndrome it may be difficult not to fudge or bluff: here the first reaction was to say that it was an extreme instance of the profuse lanugo of some ethnic groups and many preterm babies. Others in this family had been similarly misinformed and did not subsequently seek medical advice. The best paediatric policy is to admit ignorance but to correct it promptly

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Current topics

Retroviruses

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Retroviruses have assumed tremendous importance since the discovery of the viruses which cause adult T cell leukaemia[1] and acquired immune deficiency syndrome (AIDS)[2,3] The groundwork which led to the relatively recent isolation of these human viruses was laid over many years in studies of animal retroviruses, particularly those inducing leukaemia in chicken, mice, cats and cattle. The act of faith in pursuing retroviruses as causes of human disease on the assumption that what occurs in animals is likely to have a counterpart in man has, therefore, been entirely justified.

There are three subfamilies of retroviruses. oncoviruses, lentiviruses, and spumaviruses, the latter of which are not pathogenic. The oncoviruses and lentiviruses, however are of great medical and veterinary importance. The oncoviruses as their name implies cause tumours, particularly leukaemias and other diseases of the haemopoietic and lymphoid systems in man, cattle, cats, mice, and chickens. The lentiviruses include human immunodeficiency virus (HIV), which is the cause of AIDS, maedi-visna virus of sheep, equine infectious anaemia virus, and feline AIDS virus

Biology of retroviruses

Retroviruses are so called after the enzyme reverse transcriptase, which they possess and which endows them with their most important biological characteristic, the capacity to set up permanent, life long infections in their host The basis of retroviral persistence is the incorporation of the viral genes into cellular chromosomal DNA In infected cells a DNA copy of the viral RNA genome is synthesised by reverse transcriptase. This DNA is then integrated into cellular DNA as a provirus which subsequently behaves like a cellular gene. Under appropriate conditions the proviral genes are expressed and progeny virus is made without harming the infected cell. Expression of retroviral genes may be suppressed, however, by extracellular diffusible factors so that the provirus is maintained in a latent state.

A consistent feature of retroviral infections is that individuals with permanent infections may be apparently healthy for many months or years before developing a serious disease. During this extended latent period they are infectious and unwittingly may spread virus to others.

Oncoviruses

There are two main groups of oncogenic retroviruses. One comprises the leukaemia viruses of the cat. mouse, and chicken, the members of the other are the human T lymphotropic viruses (HTLV), their simian counterparts, and bovine leukaemia virus (BLV) The biology of the two groups is different in several important aspects.

Feline leukaemia virus (FeLV) is an example of the first group. The virus is transmitted congenitally across the placenta or by contact through infected saliva or milk from persistently infected animals. Some cats, especially when exposed congenitally or at an early age become permanently infected, and around 90% develop a serious and often fatal disease within three to four years. The most common related diseases are lymphoid and myeloid leukaemias, pure red cell aplasia, immunodeficiency, or infertility. These cats have large quantities of infectious virus in the blood They are immunotolerant to the virus so antiviral antibodies are not found in the serum. Most cats, however, recover from contact exposure, develop virus neutralising antibodies, and are immune to reinfection. In an endemic household about 30–40% of cats would be viraemic and the remainder would be immune

HTLV or BLV infections are rather different. While individuals may become permanently infected, the virus is not found free in the blood but is maintained in a latent state in lymphocytes, T cells for HTLV, and B cells for BLV. One of the major advances in retrovirus research was the discovery that latent virus becomes reactivated rapidly when infected lymphocytes are established for even a short period in cell culture and is detectable as infectious particles.[1] Individuals with permanent HTLV or BLV infections also make antibodies to viral proteins, unlike cats, mice, or chickens infected with their respective retroviruses. This feature is extremely important in diagnosis as antibodies are much easier to detect than latent virus The same applies to the AIDS virus HIV

Surprisingly, the methods of transmission of HTLV or BLV have been difficult to determine. Transmission is very efficient by the transfer of even minute volumes of blood. Undoubtedly, many people have contracted HTLV through blood transfusions, and cows have become infected through needles and syringes used for multiple inoculations in herds. Natural transmission may occur by biting anthropods and some cases arise by congenital transmission—and in HTLV infections, through mother's milk

HTLV causes acute T cell leukaemia in adults[4] HTLV and acute T cell leukaemia are found in several areas of the world, notably Kyushu, Shikoku, and Hokkaido islands (but not Honshu) in Japan and in the Caribbean basin In Kyushu up to 37% of adults are seropositive. Cases of acute T cell leukaemia associated with HTLV-I have been diagnosed in Britain in immigrants from Caribbean islands but the virus does not seem to have spread outside their immediate families.[5] The virus is also endemic in tropical Africa.[6] The basis of the distribution of the virus has yet to be explained satisfactorily. Unlike cats infected with FeLV, only about 1 in 2000 of people infected with HTLV (or cattle infected with BLV) develop leukaemia

The AIDS lentivirus

AIDS is currently the most important public health concern in many countries. The syndrome was first recognised in 1981 and the causative virus, now called HIV, was isolated over the following three years in France[2] and the United States of America.[3] This new disease most likely spread from Africa where the virus is now common in many areas and may have been derived from closely related simian viruses. Today transmission of HIV is by sexual contact, particularly among male homosexuals, and by intravenous drug abuse through shared needles and syringes; infected mothers can also transmit the virus congenitally to their children. Great efforts are now made to eliminate contaminated blood products which have also transmitted HIV in the past, particularly to haemophiliacs. More than one million people carry the virus in the United States of America and 25 000 people have AIDS or related conditions The estimated number of deaths in Britain is 377. The proportion of infected individuals who will develop AIDS is not yet known but could be 100%. It has been estimated that by 1991 there will be a cumulative total of more than 270 000 cases of, and 179 000 deaths from, AIDS in the United States of America. Total cases of paediatric AIDS will have increased from 300 to 3000 by that time.

Mechanisms of retroviral disease

The mechanisms by which retroviruses cause disease are rapidly being defined. FeLV and avian leucosis virus—for example, induce many cases of leukaemia by activating the cellular oncogene *myc*.[7] Consequent continuous expression of the *myc* protein seems to be an important step in the selection of leukaemic cells by maintaining infected cells in continuous growth over long periods The way in which HTLV and BLV are pathogenic is less clear: a viral gene which acts as an activator of transcription in infected lymphocytes may be important in generating cells that eventually become leukaemic.[8]

HIV infection is rather different as AIDS is caused by destruction of cells. Initially a very small proportion of lymphocytes carry the virus. Infection is restricted to T lymphocytes with the CD4 antigen. As the infection progresses, however, more T4 lymphocytes are recruited into the pathogenic process, possibly by cell fusion with infected cells Eventually so many T4 cells are lost that the function of the immune system is irreparably damaged A considerable proportion of patients with AIDS have neurological complications, of which dementia is the most severe.

Treatment, control, and prevention

One of the major challenges in medicine today is to devise methods for the treatment, control, and prevention of retroviral infections. Treatment is made difficult because the viral genome is integrated within host cells and can only be eliminated by the eradication of infected cells Some progress has been made, particularly in testing drugs which interfere with the virus specific enzyme reverse transcriptase Azidothymidine (AZT) has proved to be palliative in AIDS, but as the drug cannot eliminate virus, only halt further establishment of provirus in new cells, the treatment is incomplete. The therapeutic potential of other drugs such as ribavirin is being assessed.

Control measures are designed to interfere with the transmission cycle of virus. FeLV has been widely controlled by the isolation or elimination of carrier cats detected by showing the presence of virus in the blood.[9] This veterinary solution is obviously not suitable for HTLV or HIV. Strenuous efforts are now being made by health authorities to minimise the transmission of HIV by testing blood products for virus and by attempting to modify sexual habits and intravenous drug abuse through large scale propaganda.

Prevention by vaccination is more likely to be the method which will eventually control retroviral infections in man and animals. The first retroviral vaccine was launched in 1985 against FeLV infection and is reputed to protect 80% of cats against challenge.[10] Products designed to protect all vaccinates are being developed and are either novel adjuvants which present viral antigen more efficiently to the host's immune cells[11] or are based on genetically engineered virus or antigen which can be obtained inexpensively in very large amounts.

The same strategies are being adopted for a vaccine against AIDS. A major obstacle is that there is not an entirely suitable animal host in which to test candidate vaccines. Current studies aim to induce a demonstrable humoral or cellular immune response to HIV.

That there might be distinct serotypes of HIV has been suggested by analysis of the amino acid sequence of several virus isolates that showed differences within the appropriate antigen. Such fears have, to some extent, been allayed by the finding that antibody to any one isolate neutralises other isolates.[12] Thus there is optimism that an effective vaccine will be available in the near future.

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Human retroviruses and paediatric disease

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Retroviruses are a distinct group of RNA viruses which replicate via a double stranded DNA intermediate, synthesised from the virion by an RNA dependent DNA polymerase (reverse transcriptase). Thus unlike other viruses, exogenous RNA codes for DNA. The intermediate, known as the provirus, is integrated into host cell DNA and acts as a template for the production of viral genomic and messenger RNA by the host cell. Retroviruses are known to cause a wide range of diseases in numerous animals (Table).

In spite of an intensive search for similar viruses in man the first human retrovirus was not reported until 1980 The human T cell leukaemia/lymphoma virus type I (HTLV-1) has since been shown to be the causal agent of the adult T cell leukaemia syndrome, and more recently to be closely linked to tropical spastic paraparesis.[1] A second human retrovirus HTLV-2 is similar to HTLV-1 but has yet to be associated with disease. The third human retrovirus previously known as lymphadenopathy virus (LAV-1), or human T cell lymphotropic virus type 3 (HTLV-3), and now collectively referred to as human immunodeficiency virus (HIV), is the causative agent of the acquired immune deficiency syndrome (AIDS) and its related disorders. All three viruses have animal counterparts Retroviruses are divided into three groups: oncoviruses, lentiviruses, and spumaviruses. Oncoviruses are associated with transformation either by transporting an 'oncogene' into the host cell, or by inserting themselves next to cellular homologies of oncogenes and 'turning them on' by promotor activity. HTLV-1 and HTLV-II, although capable of causing transformation, do so by an alternative method by activating genes not necessarily next to them but at a considerable distance. This is known as trans activation, and is similar to the function of bovine leukaemia viruses of cows. HIV is cytopathic and does not cause transformation in vitro, consequently. It is similar in structure to the lentiviruses such as the visna maedi virus of sheep. Spuma or foamy viruses have been recognised for some years, although with the possible exception of Quervain's thyroiditis, they have not been associated with human disease.

The HIV family of viruses share the same general structure as other retroviruses The virion is 100 to 130 nm in diameter and contains two identical strands of RNA within a glycoprotein envelope The Figure shows the genomic structure of the HIV provirus and its products. The Gag region codes for the core proteins, the Pol region codes for the magnesium dependent reverse transcriptase, and the Env region encodes the envelope glycoproteins The Env region is highly polymorphic and may differ by 20% to 30% in different isolates of HIV. The sequences which encode the viral proteins are flanked by long terminal repeat sequences (LTRs). These regions contain promoter and enhancer elements for viral gene expression The HIV virion contains an additional four open reading frames (sequences capable of encoding a protein)

Table *Diseases caused by retroviruses in animals*

Leukaemia (avian, mouse cat primates)
Lymphoma (avian mouse, cat, primates fish)
Carcinoma (mouse (mammary), chicken, (renal) cat horse anaemia, aplasia)
Wasting and autoimmune disorders (cat primates mouse (system lupus erythematosus-like illness)
Arthritis (goats)
Nervous system (mouse, sheep goat)
Osteopetrosis (chickens)

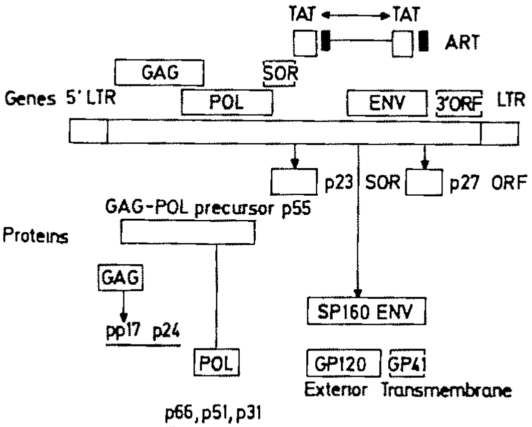

Figure *The genes and proteins of HIV*

known as sor, tat III 3'orf. and art Tat III and art both produce proteins that enhance the expression of other HIV genes—in other words they are transactivators The function of the sor and 3' orf has not yet been defined.

It is now clearly established that the T4 (CD4) molecule behaves as the receptor for HIV in human cells.[2] T4 is a non-polymorphic glycoprotein that defines a subset of lymphocytes known as helper/inducer cells which have antigen recognition and regulating function axial to the immune response. HIV binds directly to the T4 molecule via the envelope glycoprotein GP110[3] and the introduction of T4 into any human cell renders it permissive for HIV replication.[4] The T4 gene is expressed in the central nervous system[4] and probably accounts for the dual lymphotropism and neurotropism of the virus. The profound immunodeficiency found in AIDS is principally due to deletion of the T4 lymphocytes, but a wide range of immunological abnormalities are associated with HIV infections Dendritic cells and macrophages, both of which express T4, are also infected.[5] The numbers of circulating cytotoxic suppressor cells, defined by the T8 (CD8) antigen, are increased and may regulate HIV expression.[6] These abnormalities lead to a decreased blastogenic response of T lymphocytes to mitogens in vitro and cutaneous anergy to skin test antigens in vivo. Patients with AIDS characteristically have evidence of polyclonal B cell activation manifest by increased circulating immunoglobins, detectable immunocomplexes, and enhanced spontaneous proliferation and responsiveness of B lymphocytes to B cell growth factors in vitro. HIV may be a direct polyclonal activator of these cells.[7] The exaggerated B cell activity is, however, non-specific, and patients with AIDS produce a poor humoral response to new immunising antigens

Whereas HIV seropositive adults become hypergammaglobulinaemic and children often become hypogammaglobulinaemic when infected with HIV, (which may in part account for the increased number of bacterial infections in vitro). HIV seems to be able to turn on or off gammaglobulin production. Indeed, a patient who had hypogammaglobulinaemia for many years became hypergammaglobulinaemic after HIV seroconversion (Webster ADB, Spickert G, unpublished observations) B cells are probably not infectable unless they express the CD4 antigen (Malkovsky M, Dalgleish AG, unpublished observations),

The clinical spectrum of adult AIDS has been well reviewed[8] and depends in part on the range of pathogens encountered by the immunocompromised subject. The centres for a disease control definition of paediatric AIDS differ only slightly from that given for adult AIDS[9] and accept the same diseases as indicative of underlying cellular immune deficiency in both groups, with the addition of childhood interstitial pneumonitis confirmed by biopsy. Children with AIDS, however, are much more likely than adults to have intercurrent bacterial infections and may have unique pulmonary and central nervous system manifestations

AIDS in children most commonly presents with recurrent bacterial infections, often pneumonia or meningitis, persistent and recurrent oral candidiasis, and failure to thrive.[9] Almost all will develop non-specific features, including generalised lymphadenopathy, hepatosplenomegaly, recurrent otitis media, persistent monilial 'nappy rash' and diarrhoea[10] These features are familiar to the general paediatrician, and a high index of suspicion is required to diagnose an acquired immunodeficiency syndrome. In particular, the distinction between AIDS and AIDS related complex is much less clear in children than in adults Unilateral or bilateral parotid gland enlargement occurs in up to 20%, and in the context of non-specific features is highly suggestive of AIDS.

The major morbidity and mortality in paediatric AIDS is associated with lung disease. *Pneumocystis carinii* pneumonia occurrs in 30% of paediatric cases and usually within the first 6 years of life; it carries a very poor prognosis, particularly when coexistent with bacterial infection The most common lung disease, however, is chronic interstitial pneumonitis redefined by Rubenstein as pulmonary lymphoid hyperplasia.[11] This condition presents at the mean age of 14 months with radiological appearances of interstitial pneumonitis and characteristic findings on lung biopsy It is often part of a spectrum of digital clubbing, parotid gland enlargement, and raised IgG values Epstein Barr virus DNA is often found in the lung biopsy specimens[12] The mortality from this condition is 15%, in comparison with a mortality of 60% in children with pneumocystis. The manifestations in the central nervous system, which are unique to paediatric AIDS, include microcephaly, developmental delay and regression with loss of achieved landmarks, and calcification of the basal ganglia.[13] Children may also develop an encephalopathy with a combination of cortical and long track signs and ataxia, similar to the *adult* disease. Direct HIV infection of the central nervous system also probably occurs, although affected children often have antibodies to rubella, cytomegalovirus, and *Toxoplasma*. Hodgkin's and non Hodgkin's lymphomas have also been reported in paediatric AIDS. Kaposi's sarcoma occurs in less than 20% of children in most series

More than 70% of all paediatric AIDS in the

United States of America has occurred in children born to mothers who are intravenous drug abusers (Centers for Disease Control, unpublished observations). In the United States New York, Miami, and Newark have the highest number of cases of paediatric AIDS cases and have reported an approximated 50% increase for each of the past six years. It is striking that almost one quarter of paediatric cases in America have been reported by a single hospital, and it is likely that the total prevalence of the condition is grossly underestimated Maternal risk factors other than intravenous drug abuse are sexual promiscuity and regular contact with known HIV positive partners. Children may also contract AIDS from transfusion of infected blood or blood products, and more rarely from sexual abuse or needle stick injury. Medical injections may also be a risk factor in developing countries.[14] HIV is transmitted in utero and has been isolated from a 15 week fetus,[15] it may also cause a distinctive dysmorphic syndrome,[16] suggesting infection in the first trimester. HIV is also likely to be spread by exchange of maternal and fetal blood at childbirth and may be transmitted by breast milk.[17] The rate of spread from mother to child is uncertain and rates of between 50 and 90% have been reported for first and subsequent births.[9 18] The mothers of HIV positive children may be asymptomatic and may subsequently have other HIV negative children.[10] The diagnosis of AIDS in a child should therefore lead to screening of parents and siblings.

There is a single report of possible horizontal transmission of AIDS by biting.[19] Several large studies have failed, however, to show the spread of AIDS from infected to non-infected children, even in circumstances of close contact and sharing of beds, toothbrushes, and eating materials.[9 20] There is therefore no good evidence to support in any way the segregation of HIV positive children.

Laboratory diagnosis of AIDS in children is also more difficult than in adults. The profound lymphopenia of adult AIDS is absent in children. The earliest defect in cell mediated immunity is a decrease in circulating thymulin, a thymic hormone responsible for T cell maturation. B cell abnormalities are characteristically profound. Children do, however, develop antibodies to the major antigenic proteins of HIV and loss of anti-P24 may have the same predictive value for the development of AIDS as in the adult.[21] Antibodies detectable in the first 6 months of life may be acquired from the mother, and in situ hybridisation has been used in the diagnosis of neonatal AIDS.[22] AIDS must be differentiated from the primary immune deficiency syndrome, including severe combined immune deficiency (SCID), Wiskott – Aldrich and Di Georges syndrome. SCID may be an important differential diagnosis, particularly as children with AIDS are often hypogammaglobulinaemic,[10] but the distinctive clinical and laboratory features of the other syndromes should facilitate their indentification [9]

There is no effective specific antiviral drug for the treatment of AIDS. Antiviral strategy may be directed at the pathway by which the virus/T4 complex is endocytosed at the unique retroviral reverse transcriptase enzyme or at transcriptional and virus assembly control mechanisms.[23] Many *in vitro* inhibitors of reverse transcriptase exist. Azidothymidine, a thymidine analogue, crosses the blood brain barrier and has been tried in vivo It is only moderately effective and its use has been limited by severe bone marrow toxicity [24] Intravenous gammaglobulin treatment may prevent the high incidence of bacterial infection in children with AIDS [6 25] HIV positive children should never be given live viral vaccines or BCG; killed polio may be available and the triple of diphtheria/tetanus/killed polio is safe.

The development of vaccine has been based on the use of the envelope glycoproteins as immunogens. The envelope glycoprotein SP120 is highly polymorphic, and although serum from infected individuals can effectively cross neutralise different HIV isolates, no antibody raised to the envelope glycoproteins in vitro has shared this ability.[26] A vaccine using envelope glycoproteins from a combination of isolates may be more effective Alternative approaches are therefore of interest. Antibodies raised to peptide sequences from gp41 the transmembrane glycoprotein seem to have some activity against all isolates so far tested (Dalgleish *et al*, unpublished observations). Similarly, antibodies raised to monoclonal antibodies (anti-idiotypes) inhibited viral binding to T4 mol-

Provisional case definition of AIDS in children

1 A reliably diagnosed disease at least moderately indicative of underlying cellular immunodeficiency and

2 No known cause of underlying cellular immunodeficiency or any other reduced resistance reported to be associated with that disease. The diseases used as sufficiently indicative of underlying cellular immunodeficiency are the same as those used in defining AIDS in adults after the exclusion of congenital infections such as toxoplasmosis or herpes simplex virus infection in the first month after birth, or cytomeglovirus infection in the first six months after birth.

ecule and offer the exciting possibility of blocking a pathway used by every known HIV.[27]

In the meantime counselling of HIV positive patients or at risk patients is the only means of preventing paediatric AIDS. Therapeutic abortion may be offered to asymptomatic HIV positive mothers, although further information on the outcome of such progress is urgently required. Mothers with AIDS should unquestionably be offered abortion, as pregnancy is likely to be fatal for both mother and child.

Two new human retroviruses have recently been isolated. HIV-2 is described in patients with AIDS from Cape Verde, Portugal, Central Africa, and most recently, France.[28] HTLV-IV has been isolated from asymptomatic patients in Senegal.[29] These viruses have not yet been directly compared but present data show that they are both more closely related to the simian retroviruses found in old world monkeys than to HIV-1. There is no reason to believe that children will be exempt from infection by these viruses.[30–32]

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Personal view

Congenital dislocation of the hip: to screen or not to screen

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History of screening

Detection of congenital dislocation of the hip by clinical examination in newborn infants was described in 1937 by Ortolani.[1] The routine use of such an examination in all newborn babies, plus the beginning of immediate conservative management in all detected cases, was reported in 1952 by Von Rosen.[2] Von Rosen's approach promised an end to the missed late cases so often requiring multiple, hazardous, and incompletely successful surgical procedures. Indeed, in the wave of enthusiastic optimism, with which his programme was taken up in most major centres, it was expected that congenital hip dysplasia would become a condition always detected in the neonatal period and successfully treated by simple splintage within the first few months of infancy. Unfortunately, this did not prove to be the case, and although most screens provided an improvement in diagnostic success, many centres outside Sweden, continued to report undiagnosed cases. This experience was reported by Barlow in 1962 when he described a supplementary clinical test to add to the Ortolani manoeuvre.[3]

There is no doubt that Barlow's test would certainly detect unstable hips that might be missed using only the Ortolani manoeuvre, and both these tests have remained the basis of clinical screening for congenital dislocation of the hip Cases continue, however, to slip through the meshes of the diagnostic screen. Furthermore, again in centres outside Sweden, cases of proximal capital epiphysitis began to be reported This epiphysitis is the development of a Perthes like lesion in the proximal capital femoral epiphysis and is the result of splintage in abduction.[4] This is a serious complication and one that is heightened by the knowledge that many of the unstable or dislocated hips detected at birth will relocate and stabilise spontaneously without any treatment.

Timing of the screen

There have been two quite different responses to these problems among those with a special interest in congenital hip dysplasia. One response has been to attempt to make neonatal screening more successful and primary treatment by splintage safer. The other response has been to abandon neonatal screening and splintage and start a screen of all infants at 3 months of age.

I would like first to examine the second response The overriding advantage of this approach is that those cases that are to resolve spontaneously will have done so by 3 months, and these normal babies will not have been exposed to unnecessary and potentially hazardous treatment Furthermore, it is generally easier to diagnose a dislocated hip at 3 months It must be said that this is an expression, however, of the development of adaptive changes, and thus deterioration of the deformity, which could well be avoided by prompt successful neonatal splintage.

There are other problems with this approach. The results of treatment at 3 months are not as good and are probably going to require surgical as opposed to conservative management. Indeed, some of us believe that congenital dislocation of the hip that cannot be treated conservatively in the neonatal period is best managed by soft tissue release and open relocation of the hip before the onset of walking.[5] Certainly, satisfactory management in purely conservative terms is unlikely to be adequate when treatment is started as late as 3 months of age, and if it is attempted the chances of epiphysitis occurring are certainly much higher than when a child is loosely splinted in the early perinatal period.

The first response, aimed at improving the efficiency of a neonatal screen and the safety of splinting, has, I believe, the best chances of overall success in the management of hip dysplasia There are two ways in which the screen can be improved.

The first involves improvement in expertise required to carry out efficiently the clinical examination. The second involves increasing the amount of information from which a diagnosis might be made.

Improvement of expertise. The actual business of examining babies' hips at birth is often left to relatively inexperienced junior staff. With a few hours of intensive instruction from an experienced teacher, it is probably possible to make such young doctors reasonably efficient in that they will be able to pick out the obvious dislocated or dislocatable hip

Over the past nine years we have examined the incidence of congenital dislocation of the hip occurring in the newborn population of a large maternity unit with roughly 3000 live births each year. During the first two years it was obvious that some positive misdiagnoses were being made, but after the first two years the incidence fell to a steady rate of just under 1% of live births. This suggested very strongly to us that two years' experience were required to avoid making false positive diagnoses.

A similar but longer learning curve was noted in the number of cases diagnosed after the neonatal period. The first year of the study showed the number of cases diagnosed was 1·6 per 1000 live births, falling to 0·33 five years later. During the period 1983–85 there were no late diagnosed cases and in 1986 there has been one. This would suggest that our team's technique continued to improve over a period of four years. All but two of these late cases were in the high risk group, which was followed up routinely at 3 months, even though they had been found to be apparently normal at birth. These results were achieved by a team of three people that has remained the same throughout the survey. The team consists of one orthopaedic surgeon and two senior physiotherapists, who screen every live birth.[6]

Improvement of information. At present in most centres the basis of information is purely clinical and depends on interpretation of the feel of the hips on clinical examination. The very obviously unstable clunking hip is easy, but even with considerable experience the differentiation of a low pitched click from a minimal clunk can be difficult. Detection of the sliding hip, which gives a minimal sensation as it slides across the lip of the acetabulum in a lax joint, can require a high degree of clinical acumen earned by years of experience and constant practice.

Two new exciting aids to diagnosis are being developed. The first, which involves ultrasound screening of the neonatal hip, is very promising.[7] Unlike *x*-ray films, ultrasound outlines the soft tissue and is rapidly becoming more reliable as the expertise of the operators increases and the efficiency of the machines improves. The second interesting experimental approach is that of Professor Mollen from Belfast, who is using electronic visual and auditory display to give a more objective appreciation for the Barlow and Ortolani tests

Safety of splintage for congenital dislocation of the hip

Since 1977 we have not had one case of epiphysitis as a result of Von Rosen splintage, with an average birth rate of 3000 each year and an incidence of congenital dislocation of the hip of just under 1%. How is this achieved?

I believe that epiphysitis only occurs if the femoral head is jammed rigidly into the acetabulum by forcibly abducting the joint against a tight medial joint capsule. We therefore apply the Von Rosen splint in a manner that allows free movement in abduction. Only very rarely in the perinatal period is the capsule so tight that reduction is difficult, and in these rare cases the splint is not applied, the hip being left free for review at 3 months. The structures around the hip rapidly tighten up and we therefore apply the splint at 72 hours. This allows a small proportion of hips to relocate spontaneously while maintaining easy reduction without force in the remainder.

The screen

The screen that we use in my unit is similar in many respects to many others in Britain.

On day 1 each baby undergoes the Barlow and Ortolani examination of the hips. The following situations may arise.

(1) If the hips are found to be normal and the child does not fall into a high risk group the patient is discharged from follow up.
(2) If they are apparently normal but in a high risk group (breech presentation, moulding defect, or family history of congenital dislocation of the hip) they are re-examined at 3 months.
(3) If they have one or both hips dislocatable yet freely relocatable they are re-examined on the next two days. If during this time there is no change they are loosely splinted in abduction for three months and then re-examined.
(4) If during these three days the hip or hips stabilise then they are not splinted but re-examined at 3 months.
(5) Rarely one or both hips may be found to be rigidly dislocated and not easily relocatable.

In these cases splinting is not attempted and the baby is re-examined at 3 months.

Groups 2 to 5 undergo examination at 3 months. If there is a doubt or distinct suspicion of dislocation or subluxation the hips are examined under general anaesthetic and an arthrogram is carried out. If the clinical examination is apparently normal the babies are examined again at 7 months and have a single plain anteroposterior *x*-ray film taken of the pelvis with the hips in neutral position. If this *x*-ray and clinical examination yield normal results the child is checked once again at 14 months for assessment of gait. If the *x*-ray film shows a dislocation or suggests a subluxation then an arthrogram and a clinical examination are carried out under general anaesthetic. If the arthrogram carried out at 3 or 7 months shows a dislocated or subluxed hip the infant undergoes an open reduction of the hip. All these children are followed up until growth has ceased. If the arthrogram is normal when carried out at 3 months a plain *x*-ray film is taken at 7 months

We believe that this programme could theoretically be improved by adding the apparently normal babies (group 1) into the 3 month follow up. This would mean screening all babies in both the neonatal and three monthly periods. In our experience in over nine years and 28 000 births two babies with dislocated hips slipped through our screen, having been excluded from the 3 month follow up because they were apparently normal at birth and did not fall into any of the high risk groups.

Conclusion

It is possible to achieve a neonatal screening programme for congenital dysplasia of the hip that is efficient in terms of making an accurate diagnosis. It requires a dedicated, experienced, and skilful team, however, to achieve this. I have no doubt that the efficiency of the screening process can be further improved by use of the newer diagnostic aids, such as electronic augmentation for interpretation of the clinical signs and ultrasound scanning of neonatal hips. Equally, I am quite sure that these aids will not compensate for lack of skill or training in those responsible for the screen.

We have shown that with care and strict attention to timing it is possible to begin primary conservative splintage of the dislocated hip with complete safety. We feel that this really removes the main advantage gained by abandoning the neonatal screen for one carried out at 3 months of age and furthermore, dramatically improves the expectations of success

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Archives of Disease in Childhood, 1987, **62**, 638–641

Correspondence

Concern over safety of SAGM blood

Sir,

Some Regional Blood Transfusion Centres are recommending for transfusion a product in which electrolytes are suspended in a saline-adenine-glucose-mannitol medium, hence the name SAGM blood All the plasma from the donated blood has been removed, we understand, for use in the preparation of other blood products

A Medline search has not shown any reference to the safety of this product in neonates, and we are concerned because several of our members have been urged to use it Until the product has been properly evaluated in neonates, and possible side effects of its supernatant have been clarified, we would advise caution in its use even for top up transfusions Moreover, it is a wholly inappropriate product for exchange transfusions, where its use would result in total replacement of the patient's plasma by a synthetic product. This especially applies to exchange transfusions carried out to provide babies with antibodies or clotting factors in cases of sepsis or haemorrhage

We are interested to know if any readers have had experience in using SAGM blood in neonates and whether they have recognised any adverse effects

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Prolonged flare and periventricular leucomalacia (PVL) in preterm neonates

Sir,

We read the paper by Trounce *et al*[1] with interest In this article periventricular leucomalacia (PVL) was divided into three appearances cystic, precystic, and 'prolonged flare' The latter was defined as an appearance of relative increased echodensity in the periventricular region seen both in coronal and parasagittal views and persisting for at least two weeks but not undergoing cystic degeneration

We wonder whether this term 'prolonged flare' comprises only 'large intraparenchymal echodensities', as defined by McMenamin *et al*[2] and 'globular, blotchy, coarse echoes', as defined by DiPietro *et al*,[3] or whether it includes also 'small intraparenchymal echodensities'[2] and 'peritrigonal echogenic blush'.[3] According to the necropsy results, infants with the latter two findings may or may not have PVL [2 3]

In some cases this 'blush' disappears when the scan is obtained through the posterior fontanelle. The best explanation for it could be the interface of numerous parallel fibres that are nearly perpendicular to the longitudinal axis of a sonographic beam passing through the anterior fontanelle [3] In other cases it does not disappear and these might be those with PVL On the other hand, a large and globular, coarse periventricular echodensity, often unilateral, may more likely be an ultrasonic manifestation of focal hypoxic-ischaemic lesion caused by a hypotensive insult, than PVL, which is usually bilateral

The duration of echodensity indicating PVL is the other problem Why did Trounce *et al*[1] prospectively, as they say, choose two weeks for it? Why not four weeks? Was this choice arbitrary or was it based on some clinical follow up results? If it was based on necropsy findings they do not provide any reliable answers as far as surviving neonates are concerned

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Drs Trounce, Rutter, and Levene comment

Thank you for your interest in our paper The question is that of comparison between our definition of 'prolonged flare' and alternative definitions by other groups At the outset of our study (1983) we defined carefully a variety of ultrasound appearances We were aware of McMenamin's definition but that of DiPietro *et al*[1] has only recently been published and was not available to us originally, or before we submitted our paper for publication to the *Archives of Disease in Childhood* We have been impressed, on scanning many hundreds of infants, that persistent echodensity in the periventricular white matter is a common finding and is often normal, particularly when the occipital region is affected We rarely saw this appearance in two planes, however, and if it did appear on coronal and parasagittal section it was usually transient, lasting only for a few days

Our rigorous definition of prolonged flare was developed so that most of these appearances would not be included On careful reading of the paper by DiPietro *et* *al*,[1] it would appear that this 'blush' is only diagnosed on parasagittal section This is therefore not at all comparable with our definition. which must be seen on two planes In addition, these authors give no information on how long the echos were required before they considered the blush to be abnormal. Indeed, the babies died largely within a few days of age, so clearly this would not fit in with our definition It is, however, interesting to note that the prevalence of PVL in 68 consecutive liveborn infants dying under two months of age in their unit was 26% This compares very favourably with the 25% incidence of PVL that we recognised prospectively using ultrasound on our 200 very low birthweight babies

The point of our study was to set up a prospective database of 200 infants who were scanned sequentially and in whom there was clear understanding of what we meant by our ultrasound appearances Our definitions were, of course, arbitrary as we did not have the benefit at that time of clinical follow up We have now completed follow up collection on all the surviving infants and the relevance of our definition of prolonged flare will hopefully soon become apparent.

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Tracheobronchial suction in ventilated neonates

Sir,

We congratulate Dr Prendiville *et al* on their successful attempt to investigate the efficacy of tracheobronchial suction in ventilated neonates.[1] This aspect of the routine care of ventilated babies has important consequences Knowing when, how often, and how to perform endotracheal tube toilet is difficult, and their study provides some of the answers Unfortunately, continuous monitoring of airways resistance by flow-volume integration using a double pneumotachograph system seems unlikely to be practical for routine clinical use

The single breath technique for determining airways resistance relies on passive expiration Most ventilated babies with the respiratory distress syndrome make use of their abdominal muscles to expire actively (South M, Morley C J Expiratory muscle activity in premature babies Presented to Neonatal Society, November 1986) The authors state that spontaneous respiration was stopped by increasing ventilator rate This is unusual in our experience We find that at faster ventilator rates most babies continue to breathe spontaneously but synchronously with ventilator inflations [2] When breathing synchronously, they can seem to be apnoeic, with linear flow-volume curves Expiratory muscle activity often continues during synchronous breathing, and this could shorten expiratory time constants and reduce the calculated resistance Despite these reservations we are sure that the results of this paper are helpful We would recommend, however, that an independent method for detecting the presence of spontaneous respiration should be used.[3]

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Infantile colic and feeding

Sir,

Unfortunately the paper by Stahlberg and Savilahti[1] adds to the confusion that already exists regarding an association between infantile colic and cow's milk.

They failed to define colic and, therefore, the criteria for entry into the study The mean age of the babies at entry was nearly 3 months by which time a large number of babies with 'colic' will be improving spontaneously The duration of feeding on each milk preparation was too short to show any important differences, and there was no washout period between each milk, with the likelihood there will be a carry over effect from the preceding preparation

Analysis of the data in Table 1 in their paper shows that eight of the ten babies received breast milk first with or without the lactase so that the results do not report adequately on the relative impact of formula followed by breast milk In addition, if the data are analysed by order of administration of treatment[2] the proportion of days with colic declines from 86% for the first treatment, through 81% and 79%, to 74% for the last treatment given There is, therefore, a clear trend of improvement over time so that treatments given first tended to do badly

The small size of the study also gives cause for concern The authors conclude that 'infantile colic is not a symptom of lactose malabsorption' It is doubtful whether the study could have provided adequate statistical power to detect any true differences that may exist. Finally, a repeated measures analysis of these data should have been done, rather than the statistically invalid methods used in the paper

It is only by an appropriately designed trial using an adequate sample size that the question of an association between cow's milk and infantile colic may be answered

References

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Dr Stahlberg comments

The definition of colic was stated in the introductory lines; the healthy babies had expressed colic of three to 13 hours' duration daily, only cases 2 and 6 occasionally having had daily colic of shorter duration than three hours, washout periods have no relevance in this context, any food between treatments might produce carry over effect, professional statisticians were consulted about proper statistical methods

Based on previous reports[1-3] we decided that one week on each milk preparation should be sufficient for spontaneous recovery We knew that only in 50% of infants would colic resolve by the age of 3 months, particularly children with severe colic who may have extended duration of the problem

Cases 2 and 9 provided a slight decline in the overall percentage of symptomatic days Most days colic was present even during the last treatment A closer look at the information provided in the Tables shows that two children had their longest daily colic during the first treatment, four during the second treatment, two during the third treatment, and two during the last treatment. Three children had their shortest daily colic during the first treatment, three during the second treatment, one during the third treatment, and three during the last treatment. A systematic error by order of treatment is therefore definitely ruled out

We are sorry for confusing those who were satisfied with the present knowledge about the aetiology of infantile colic. We feel that colic is not a uniform entity nor that milk is the universal cause of the problem Unfortunately, formulas free from cow's milk are now commonly and uncritically given to infants with colic by health professionals and laymen

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Chromosomal defects and caesarian birth

Sir,

In their interesting article Dr Young *et al* provided further evidence that infants with trisomy 18 are often born by caesarian section.[1] Chromosomal defects were diagnosed after birth in 19 of 1411 infants weighing 501–2000 g liveborn to Merseyside residents in 1979–1981. Eleven (58%) of the 19 were delivered by caesarian section—five elective and six during labour—compared with 27% of the other infants ($p<0·01$)

The increased risk of caesarian birth was significant after allowing for birth weight, gestational age, and sex ($p<0·05$) The risk, however, applied not only to infants with trisomy 18 (five of eight) but also to infants with other chromosomal defects (six of 11 infants) These comprised all infants with monosomy 4p (n=1), trisomy 4p (n=1),[2] ring 13 (n=1), and trisomy 13 (n=1), and two of seven with trisomy 21.

The risk was related to severe growth retardation the birth weights of nine of the 11 born by caesarian section were below the 5th centile for gestational age compared with two of the eight born vaginally ($p<0·05$); trisomy 21 was not associated with severe growth retardation as often as the other defects Infants with chromosomal defects had lower 5- and 10-minute Apgar scores than other infants ($p=0·023$ and $p=0·011$, respectively), associated cardiac defects may increase the risk of fetal distress and obstetric intervention.

The authors point out the potential value of a safe means of rapid fetal karyotyping in late pregnancy, when growth retardation or hydramnios raise suspicion of a severe congenital defect Our low birthweight sample, however, contained 560 growth retarded livebirths (birthweight <10th centile for gestational age) of which only 13 had diagnosed chromosomal defects Would ultrasonography for cardiac defects help to narrow the field?

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Phosphatidylglycerol in tracheal aspirates for diagnosing hyaline membrane disease

Sir,

In a recent paper,[1] we showed that the simple and rapid determination of phosphatidylglycerol (PG) in tracheal aspirates, for the diagnosis of hyaline membrane disease, was more sensitive (97%) than the lecithin sphingomyelin (L:S) ratio (88%), with a similar specificity (76%) It seems to us, however, that the discrepancy between biochemical tests and clinical diagnosis was observed particularly in the lowest gestational age newborns.

Accordingly, we studied PG and the L S ratio in 149 newborns with respiratory disease (term, 26 to 42 weeks) to determine whether there was a correlation between the results and the gestational age

For the L S ratio, the results did not depend on the gestational age The sensibility and specificity of this test were 91% and 74%, respectively With the determination of PG, however, the results depended on the gestational age For newborns with a gestational age of 31 weeks or more, the sensibility and specificity of PG determination of hyaline membrane disease were 100% and 77%, respectively For newborns with a gestational age of less than 31 weeks, the sensibility was the same by both methods (91%) but the specificity was only 30% with the PG test

In conclusion, in newborns with the lowest gestational age (less than 31 weeks) estimation of the L S ratio is preferable to PG determination for the diagnosis of hyaline membrane diseases As for other newborns, given its simplicity, rapidity, and reliability, PG determination can be regarded as a useful method for the diagnosis of this respiratory disease

Reference

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Nebulised beclomethasone dipropionate suspension

Sir,

We were interested to read the comments on our two papers[1 2] by Dr Clarke[3] but consider that he has overemphasised the differences between our two publications [1 2] As he points out, although the paper of Storr *et al* showed a significant response to treatment with beclomethasone,[2] the study of Webb *et al* showed similar trends, although these failed to reach significance [1] Secondly, the children studied by Webb *et al*[1] almost certainly had more severe asthma as one of the entry criteria was a failure to respond satisfactorily to treatment with nebulised sodium cromoglycate.

We agree, however, that beclomethasone dipropionate given as a nebulised suspension to preschool children is less effective than the same drug given by rotahaler or aerosol to schoolchildren with asthma

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Cooperation on developmental assessments

Sir,

I wonder if through your columns I can make a plea for more cooperation between assessment centres attempting to meet the developmental and educational needs of children and research teams from neonatal departments

I have recently, on several occasions, found it impossible to make any meaningful assessments of children because I discover that within the previous few weeks a research team from the hospital where the child was born has contacted the parents, known of our involvement, but not contacted us before going in and performing various standardised tests, which then cannot be repeated as part of the child's normal routine assessment for his care We then do not have any results from this testing and cannot perform our own because of it

I am perfectly happy, with the parents' permission, to make results of our assessments available to research teams, but I really feel that it is to the detriment to the child if they insist on working in isolation

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Book reviews

Retinopathy of Prematurity. Current Concepts and Controversies. Edited by A R McPherson, H M Hittner, F L Kretzer. Pp 225· £40·50 hardback B C Decker Inc. 1986

This well produced, slim volume is largely the work of the ophthalmological group at the Cullen Institute at Baylor College of Medicine, Houston, Texas While there are guest contributors from Israel and Japan, 11 of the 19 contributors come from Texas This makes for some internal consistency in the book but leaves the reader with some concern that there is too much inbreeding and unified support for the spindle cell hypothesis, the efficacy of treatment with vitamin E, and surgical cryotherapy, all of which might not receive wholehearted support among other groups of experts from elsewhere in the world.

Despite the major contributors coming from the single centre in Houston, there is a rather disappointing lack of coherent editorial control, with unnecessary historical repetitions and chapters coming entirely out of any logical order

The book falls into four sections: the three first chapters represent basic considerations, which occupy 12% of the book, a second section deals with mixed considerations from retinal development to medical legal reflections, occupying 23% of the book; a fairly intense third section on treatment with vitamin E makes up 16% and a rambling, poorly edited, and over illustrated final section of the book deals with surgical approaches to retinopathy of prematurity, occupying the remaining 48%

There are now so many publications on retinopathy of prematurity, and it remains a subject of such perennial importance in the care of the newborn infant that a text of this type is in many ways to be welcomed Within it there are some brilliant pieces, to my mind the modest chapter on classification of retinopathy of prematurity by Kingdom from Florida is the high point of the text, making it crystal clear that with properly applied indirect ophthalmoscopy it is possible to describe the state of the premature retina in such a way that this could be agreed internationally, showing stages of abnormal vascular proliferation assigned to zones and quadrants of the retina in a quantitative fashion. This degree of precise classification should represent the essential currency of clinical trial reporting and honest brokerage in this difficult field, and I am not sure that other chapters in the book come up to the requisite standard.

A second excellent essay tucked away between animal models, efficacy of treatment with vitamin E, and toxicity of vitamin E is a short piece on the current state of the ethics of future experimentation in the field of treatment with vitamin E This piece by Brody from Houston states the regrettably familiar position with marvellous clarity In his view treatment with vitamin E has gone too far for further randomised controlled trials to be morally permissible While he clearly regrets this position, he nevertheless carried me with him on two counts Given the background knowledge and the outcome of the early studies there is an indication, falling short of proof, that there is some benefit and little risk attached to treatment with vitamin E More convincingly, however he argues that enrolment in a trial must depend on informed parental consent and that anyone offering parents a balanced set of information about the state of the current art would surely fail to recruit further subjects for any trial He concludes that this is a classic conflict of interests between those of society in clarifying our state of knowledge and those of the individual patient seeking the best care available.

In the first half of the book there are a number of pieces that clearly represent the major motivation of the three editors in producing this book It provides the forum to present their unifying hypothesis that all the strands in the retinopathy of prematurity story can be brought together if the condition is understood in terms of the vulnerability of the spindle cell to oxidative damage and the production of angiogenic factors This hypothesis is richly illustrated and supported by morphological and immunocytochemical illustrations largely from the authors' database of 97 pairs of premature baby eyes on which their thesis is based. Impressive as the work is, they lost a little support as far as I was concerned in adding a chapter on animal models and arguing that neither the baboon, puppy, or rat were suitable animal models because they did not have a spindle cell population of equivalent maturity to the human. Somehow this had a self fulfilling prophetic ring to it, and I would like to have seen critical sections from other centres to make sure that the ophthalmological fraternity as a whole would support this general viewpoint

The vitamin E chapters suggest that the published works have now clarified the position of treatment with vitamin E and it goes so far as to set out a clear therapeutic schedule On the other hand, at least in the section on biomedical ethics we are told that opposing views do exist from the research group in Los Angeles The editors would have carried more conviction if they had invited a Los Angeles viewpoint into their midst.

By the time I reached the second half of the book I have to confess that my interest began to flag The invited chapter from the Bailinson Hospital in Israel on cryotherapy in preventing severe visual handicap in low birthweight survivors was well written at least The argument put forward is that the absence of blindness among the 942 low birthweight survivors argued the case for the efficacy of selective cryotherapy without the need for a control group The authors were sufficiently convinced that they would consider it unacceptable to participate in a randomised control trial in the future. But what a pity this is, given the perfect arrangement that has been used to such advantage in diabetic retinopathy of having two eyes in each patient with which to design the clinical trial. Given the precision of the early chapter on classification of the disease I wonder how the Bailinson group or the other surgical groups that contribute to the text defined their criteria for intervention in the first place. The other surgical chapters deal with techniques of surgery, including open sky vitrectomy, scleral buckling, cryotherapy, and photo-coagulation There seems to be a general concordance that treatment is successful but by this stage in the book I was suspicious that the contributors had been selected to present a unified front

The text is well printed and easy to read with large numbers of high quality drawings and black and white photographs I found it a source of great disappointment that in some of the key early sections of the book there were no colour photographs of the retina in a subject that so perfectly and importantly lends itself to colour illustration. How frustrating to find then right at the back of the book a series of gorgeous coloured photographs tucked away as colour plates out of context

This is a book for the library and not for the individual paediatrician But, perhaps of greater importance, it might be taken as a challenge to British neonatal medicine and neonatal ophthalmology to define our own database and current state of good clinical practice in the prevention and management of retinopathy of prematurity

DAVID BAUM

Recent Advances in Paediatrics. Vol 8 Edited by R Meadow Pp 284. £28.00 hardback Churchill Livingstone, 1986

'Recent advances in paediatrics' is now in its eighth edition and Roy Meadow has again put together 15 chapters of topical interest to bring us up to date in various fields As always, the reader will find more of interest in one chapter than another but on this occasion he will find most subjects of practical everyday importance, and there will be something new to be learnt in most.

The acquired immune deficiency syndrome starts off the book and Drs Jones and Watson give a comprehensive review of the subject up to the time the manuscript was written The field is changing so rapidly that perhaps a short update should also be included in the next edition The same applies to the third chapter on growth hormone deficiency, again a rapidly developing field where growth hormone is being considered for differing groups of patients Professor Milner and Dr King have carefully reviewed their subject, although I feel that the section on anthropometry was perhaps a little short compared with the amount of space related to biochemical tests.

The chapters on single dose treatment of urinary tract infection, neonatal jaundice, hearing screening in the newborn, near miss cot death, and idiopathic thrombocytopenic purpura were all excellent, with up to date information and practical advice They should be read by all practising paediatricians Those chapters on modern diagnostic imaging and Doppler echocardiography are fairly technical but an education on developing fields of paediatric practice I also like the detective story of Indian childhood cirrhosis

Child psychiatry is very much part of paediatrics and the two chapters on anorexia nervosa and child sexual abuse discuss these subjects in depth and are practical in approach

The eighth edition of this book should be put on the working shelf next to the seventh edition

P R BETTS

Connective Tissue Disease: Molecular Pathology of the Extracellular Matrix. The Biochemistry of Disease Vol 12 Edited by J Uitto and A J Perejda Pp 553 $94·75 (USA/Canada), $113·50 (all other countries) hardback Marcel Dekker, 1987

Connective tissue is a complex mixture of components, including collagen, elastin, proteoglycans, and various adhesive proteins such as laminin and fibronectin Widely distributed in structures such as bones, arteries, tendons, basement membranes, skin, intestines, pleuroperitoneal lining, joint capsules, and cartilage, there is limitless opportunity for inborn inherited and acquired diseases These can commonly present to paediatricians in children of all ages Obvious examples include osteogenesis imperfecta, congenital arterial fragility, and various subgroups of epidermolysis bullosa

The book authoritatively covers connective tissue biochemistry, histology, and electron microscopy, and clinical aspects include collagen fibril variations in Ehlers-Danlos syndrome and osteogenesis imperfecta, the molecular pathology of fibrotic diseases such as pulmonary fibrosis, and normal healing Basic information on collagen protein structure and assembly, elastin and microfibrillar structure, organisation of basement membranes, and adhesive interactions are well covered and presented, but there is only scanty information on the molecular biology of collagen

This is a work for basic scientists and researchers with a special interest in connective tissue structure rather than the practising clinician Nevertheless, the relevance of basic science to clinical practice is very well illustrated by this book The price and detailed basic science will probably limit this book to the libraries of academic physicians, rheumatologists, dermatologists, geneticists, and basic scientists interested in this rapidly expanding field.

F M POPE

Clinics in Oncology. Late Effects in Successfully Treated Children with Cancer. Vol 4 No 2 Edited by M E Nesbit Jr Pp 195–355 £15·00 hardback W B Saunders Company, 1985

The aim of treatment of childhood cancer is a healthy well adjusted adult Unfortunately, the treatments used in malignant disease give rise to physical and psychosocial side effects, many occurring after treatment has finished This book collects together the experience of several centres and discusses the late side effects that occur

Chapters are divided into those dealing with dysfunction in organ systems and those concerned with the adverse effects seen in particular malignancies—for example, acute lymphoblastic leukaemia, Ewing's sarcoma, etc. Second malignancies and problems encountered in the patients' offspring are also covered

There is much useful information contained in this book with many of the references relating to the 1980s

Psychosocial aspects are covered but not as fully as physical problems and the authors emphasise the need for further studies in this field All the authors save one hail from North America This is most noticeable in the chapter on the role of the nurse in late effect evaluation, and though some of the information will not be applicable in all countries, the chapter contains much sensible advice on monitoring the child and aiding and educating the family

This book gives an interesting and useful overview of the problems that need to be considered in any child treated for malignant disease It is reasonably priced at £15

A ESSEX-CATER

Atlas of Skeletal Dysplasias. By R Wynne-Davies, C M Hall, A G Apley Pp 646 £95 00 Churchill Livingstone, 1985

Some books, like people, have more quality the more we know of them *Atlas of Skeletal Dysplasias* is so, it feels good, it looks good, and it is good.

Assembled by a threesome of orthopaedic geneticist, paediatric radiologist, and orthopaedic surgeon, it is a collector's catalogue of bone dysplasias from the cradle to the grave, arranged in order of the principal feature of the dysplasia

The text is succinct and informative, the style granite, the result, an accessible bran tub with a few up to date references on each dysplasia and helpful cross references in the index—for example on bow legs, cone-shaped vertebral bodies, or short metacarpals The clinical photographs, growth charts, and comparison of *x*-rays of—for example—hands or pelvis at similar and differing ages in different patients emphasise the astonishing variety in each dysplasia.

All who are puzzled by problems of failure to grow or short stature will be grateful to the authors for sharing their long and profound experience with those of us who see but a few patients Their Mrs Beeton of bone dysplasia will amplify the standard references—Spranger, Langer, and Weidman's *Bone Dysplasias* and Smith's *Recognisable Patterns in Human Malformation*

Alas, there is a problem. Some of the illustrations do not show what their captions declare, particularly the infant's skulls and lateral spines; perhaps these can be improved in the next edition. It is a pity too that there are no captions beneath the introductory normal *x*-rays Why no mention of idiopathic bow legs under metaphyseal dysplasia? Do the authors still advise babygrams? It would have been helpful to have a list of conditions diagnosable at birth.

But one likes a friend better for having faults one can talk about, I can enthusiastically welcome this book and recommend it to all paediatricians A Mrs Beeton with four eggs, a rich diet indeed but digestible

SIDNEY SMITH

Sonography of the Infant Hip: an Atlas. By Reinhard Graf and Peter Schuler Pp 276 DM150 hardback VCH Verlagsgesellschaft 1986

One of the initial troubles with ultrasound examinations is the difficulty in endeavouring to relate the images produced to anatomy and pathology Most find a period of apprenticeship the easiest way to overcome this problem The applications of ultrasound to that eminently suitable subject, the young child, continue to increase. This timely publication allows one to share the experience of pioneers of sonographic examination of infants' hip joints

The book is essentially a profusely illustrated atlas of the normal and abnormal appearances of the hip joint, with clearly annotated anatomical details Introductory chapters provide photographic illustration of the correct positioning and scanning techniques, with sections on instrumentation, adjustment, and documentation The first half of the book is essentially descriptive, in which the spectrum of acetabular dysplasia and hip dislocation is well presented The second half of the book is mostly concerned with the quantative evaluation of hip sonograms, with associated angular measurements, which Dr Graf in particular has developed

Not all ultrasonographers would feel inclined to use this technique or abide by the classifications, but the qualitative value of the illustrations in these sections remains useful and informative, and as a practical atlas the work can be commended

D G SHAW

Correction

An error occurred in the paper entitled 'Aetiological factors in leukaemia and lymphoma', by McKinney, Cartwright, Saiu, *et al* **62**:279–87

Throughout this paper, for the term 'common null cell acute lymphoblastic leukaemia' please read 'common acute lymphoblastic leukaemia'

This error occurs only in the context of this paper

Archives of Disease in Childhood, 1987, **62,** 645–652

British Paediatric Association

Annual General Meeting, University of York, 7–10 April 1987

Abstracts for plenary spoken sessions

Liver transplantation – Cambridge/King's Series. S Pett, A Pelham, J Tizard, N Barnes, G Mieli-Vergani, A P Mowat, R Williams, K Rolles, and Sir Roy Calne (Cambridge and London).

Between December 1983 and August 1986, 84 children were assessed for possible liver transplantation. Eighteen, mainly infants with biliary atresia, were not accepted because of features which made successful transplantation unlikely Four children were withdrawn from the programme by their parents; nine died before a donor of suitable size or compatible blood group could be found, nine await transplantation, nine have been accepted for liver transplantation but are at present sufficiently well for this to be postponed Thirty five, aged 7 months to 16 years, had liver grafts. Of these, 17 had biliary atresia, eight cirrhosis following hepatitis in infancy, five fulminant or subacute hepatic failure, three malignant liver tumours and two metabolic disease Fifteen died, nine in the first two months mainly from primary graft failure or vascular thrombosis, later deaths being due to rejection, infection, or dissemination of malignant disease. Two died of disease in other organs with a normally functioning transplanted liver, two of the survivors have had a second liver transplantation. Three have significant hepatobiliary problems which may require retransplantation. The majority of survivors are engaged in normal activities for their age, growing and developing satisfactorily with normal biochemical tests of liver function and complete regression of cirrhosis. Their excellent quality of life is encouraging. Lack of donors, particularly for young infants and prevention of postoperative rejection and infection are continuing problems.

Congenital AIDS: experience in The Bahamas. H Howard-Gardiner (Bahamas).

Following the availability of a diagnostic test for AIDS at the Princess Margaret Hospital, Nassau, in June 1985, 27 children were found to be seropositive during the following 13 months. They were born to 18 mothers, 14 (78%) of whom were from Haiti. Nineteen (70%) of the children were of Haitian origin. Sixteen mothers were seropositive and symptom free. Two were not tested, one dying earlier from salmonellosis The age at diagnosis of the 27 children ranged from birth to 6 years. Twenty three were symptomatic and the remaining four were identified during family screening. After the birth of a positive child in a family all subsequent children in this series were seropostive, although one identical twin did not develop antibodies until 18 months of age. All the 19 children with clinical AIDS became symptomatic within 18 months of birth and suffered from repeated bacterial infection of the respiratory or gastrointestinal tracts; 74% failed to thrive; 47% developed chronic lung disease; and 63% persistent candidiasis. Survival time from the onset of symptoms among the nine (47%) that died during the study period ranged from two weeks to three and half years. Four other seropositive children (2–6 years old) were in the prodromal phase in July 1986.

Prospective trial of operative (Op) versus non-operative (N-op) treatment of vesico-ureteric reflux (VUR): five years' observation. C M Taylor (on behalf of the Birmingham Reflux Study Group).

The study design and results of two years' observation on 96 children were reported previously.[1] Analysis now extends to 161 children followed up for two years, of whom 104 were followed up for five years. VUR was abolished in 98% of Op cases, whereas grade III VUR persisted in 56% of N-op ureters at two and five years. One Op and one N-op patient progressed to endstage renal failure, and another four with bilateral scarring were hypertensive.

Between treatment groups no significant differences were found in incidence of urinary tract infection, 51 Cr-EDTA slope clearance, overnight urine concentration, renal growth, scar progression, or new scar formation. Ten new scars developed in patients aged 2–7 years at entry but only during the first two years' observation. Scar progression occurred at all ages and was significantly more in the first two years' observation.

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[1] Birmingham Reflux Study Group Contributions to Nephrology *Reflux Nephropathy Update* 1983;**39:**169–85

Neither treatment fully protects against further renal damage, and efforts should be directed to identifying those at risk before scarring develops.

Randomised trial of four anticonvulsants in the newborn. M J Rochefort and A R Wilkinson (Oxford).

Seizures in the newborn are common and often difficult to control despite loading doses of phenobarbitone or phenytoin of 20 mg/kg. When control is not achieved within five days, there is a significantly worse outcome. In a randomised trial of four anticonvulsants seizure diagnosis and control were based on continuous EEG monitoring. The drugs and loading doses used were: phenobarbitone (20 mg/kg); phenytoin (30 mg/kg); clonazepam (0·2 mg); sodium valproate (10 mg/kg). In all four groups the loading dose was repeated three times in the first 24 hours if seizures continued, and then another anticonvulsant added if necessary. Babies were monitored for a minimum of five days. In 18 months 68 babies at high risk for neurological dysfunction were monitored for seizures and 26 babies have been entered into the study with parental consent (Table).

Drug No (died)		*Pheno-Barbitone*	*Phenytoin*	*Clonazepam*	*Valproate*
Weight (g)	Mean (SD)	1969 7	2749 4	2627 5	2 70 2
		1016 7	933 9	1366 8	1 59 3
	Range	624–3602	789–[illegible]434	975–4110	[illegible]73–3750
Time to control Hours	Mean (SD)	127 7	43 5*	98 7	48 5*
		53 5	50 [illegible]	76 5	59 5
	Range	55–120	10–[illegible]2	12–120	14–120

*Values are significant at p<0 05, compared with phenobarbitone (Babies seizing after five days were coded as 120 hours).

This study confirms that babies with neonatal seizures have a high mortality. Control of seizures may be improved by the use of drugs other than phenobarbitone.

Early immune changes before the diagnosis of insulin dependent diabetes. D Vergani, A Millward, M J Hussain, R Gledhill, G F Bottazzo, D A Pyke, and R D G Leslie (London).

In order to discover how early immune changes can occur before the onset of insulin dependent diabetes we studied prospectively non-diabetic identical twins of insulin dependent diabetics. The twins were examined for the presence of autoantibodies to islet cells and insulin and activation of T lymphocytes expressing the HLA-DR antigen. Results were compared with those in the controls of similar age and sex. Of the non-diabetic twins, seven developed diabetes (median age at diagnosis 14, range 12–27 years, 4 females). The seven twins were tested on 40 occasions between 0·5 and 11 years before the onset of diabetes when the fasting blood glucose was normal. Complement-fixing islet cell antibodies were found in all seven twins when first tested and four also had insulin autoantibodies. In addition, all the twins, when tested 0·5 to three years before diagnosis, had levels of activated T lymphocytes above 0·4%—that is, above the control range. In conclusion, we have shown that immune changes can occur up to 11 years before the onset of insulin dependent diabetes, and involves activation of both B and T lymphocytes.

Outcome of childhood herpes simplex virus encephalitis. P Habibi, H Holzel, E Brett, J Wilson, and R Levinsky (London).

Twenty cases of herpes simplex virus encephalitis (HSVE) have been diagnosed at our hospital over the past 12 years. Seven received antiviral therapy with acyclovir, while the other 13 were treated supportively, or also received therapy with adenine arabinoside. The overall mortality was 20%, but no deaths occurred in patients treated with acyclovir. The outcome in the survivors was better in the acyclovir group, but in all cases, depended on the level of coma at diagnosis. When the interval between presentation and commencement of antiviral treatment was greater than three days, the survivors were severely neurologically handicapped. Prompt diagnosis was aided by the use of neuroradiology and electroencephalography. Confirmation in all cases was by antibody conversion and/or by isolation of the virus from brain tissue. Fourteen had CT scan abnormalities suggestive of HSVE, but in five the initial CT scans were normal. The first EEG was abnormal in all cases, but in three the findings were initially not typical of HSVE. Brain biopsy provided early confirmation of the diagnosis in three cases. Since brain biopsy is so invasive and as acyclovir is a safe effective drug for herpes simplex virus, early treatment is recommended even on suspicion of the diagnosis of HSVE.

The development of 'targeted' radiotherapy to treat central nervous system tumours. L S Lashford, H B Coakham, A G Davis, and J T Kemshead (London and Bristol)

Considerable progress has been achieved in the control of central nervous system tumours by the judicious use of radiotherapy. However, effective employment of this treatment may damage the developing child and result in both impaired growth and intellectual development. A strategy for dealing with this problem is to attempt the 'targeting' of radiotherapy to tumour deposits using monoclonal antibodies To investigate the feasibility of this approach the intrathecal administration of radiolabelled antibodies has been explored in both non-human primates and patients with leptomeningeal tumour. The studies have taken two forms: (i) an investigation of the biodistribution of tumour binding and non-binding antibodies; and (ii) a pilot study of high dose 131-I monoclonal antibodies in patients with leptomeningeal tumour. From this work it has been possible to demonstrate that a uniform distribution of 131-I monoclonal antibodies can be obtained within the subarachnoid space. Non-binding antibody is rapidly cleared from the central nervous system and appears as intact radiolabelled antibody within the vascular compartment In the presence of tumour it is possible to obtain selective binding of antibodies to tumour and these 131-I monoclonal antibodies stay in association with tumour for many days Patients with relapsed leptomeningeal tumours have tolerated up to 45 mCi of 131-I intrathecally with minimal acute toxicity. Four to five therapeutic responses have been obtained. This new approach to the delivery of neuraxis radiotherapy appears effective, and is likely to be a less toxic form of delivering radiotherapy CNS lymphoma, leukaemia, and medulloblastoma are all amenable to this approach.

Preschool vision screening: a case for rationalisation.
S L Stewart-Brown and M N Haslum (Bristol).

We report the results of a survey of preschool vision screening practices in the 165 health districts of England and Wales: the survey was undertaken at the end of 1984 and the response rate was 81·3%

A remarkable range of tests were reported to be in use, applied at a variety of ages from 3 months to 5 years. Two districts reported carrying out no preschool vision screening at all, while 36 districts aimed to test all childrens' visual acuity on three or more occasions, and 38 aimed to perform cover tests this frequently Thirteen different types of acuity test and 10 different types of ocular muscle balance test were in use. Only 25% of districts were able to report the proportion of children cover tested in the previous year and only 10% the rate of referral to investigation from their screening programmes.

Research into visual acuity screening in infancy has demonstrated its lack of efficacy Results from trials of treatment for amblyopia and squint have cast doubts on the value of screening programmes for the detection of these conditions. The principal challenge for the Child Health Services in the 1980s is to find ways of rationalising ineffective and expensive activity. Preschool vision screening would appear to be a good place to start.

Gastro-oesophageal reflux in the preterm infant.
S J Newell, M E I Morgan, G M Durbin, and I W Booth (Birmingham).

The incidence, severity, and natural history of gastro-oesophageal reflux (GOR) in preterm infants is unknown. We have therefore studied GOR in the neonatal intensive care population. Continuous intraoesophageal pH was monitored over 24 hours using a novel 1 mm antimony pH electrode (Synectics Medical) Electrode position was determined by manometry and the lower oesophageal sphincter pressure (LOSP) measured. Fifty one measurements were made on 29 patients (post-conceptional age (PCA): 26–39 weeks). They had (mean ± SEM) 12·1(2) episodes of GOR per 24 hours. Intraoesophageal pH was 4 for 4%(0·9)% of the total time. The longest episode during each recording was 17(4·6) minutes

GOR was most likely to occur at the time of physiotherapy, oropharyngeal suction, and nappy change ($p<0·001$), and was also increased postprandially ($0·05<p<0·1$). Reflux was increased to a lesser extent in the left lateral position compared with a right lateral and prone positions. There was no correlation between GOR indices and PCA, gestation, or LOSP. Infants receiving xanthine for apnoea had a two-fold increase in GOR ($p<0·05$). A subgroup of six infants with recurrent apnoea unresponsive to xanthine had markedly more severe GOR than all other infants studied ($p<0·001$). A rapid reduction in the frequency of apnoea followed abolition of GOR with thickened feeds.

In the neonate GOR has been implicated in pulmonary disease and recurrent apnoea. We have found that GOR is common in the preterm baby, and have defined a number of predisposing factors with consequent implications for nursing care. We have also found an important subgroup with severe symptomatic disease which may be successfully treated.

Testosterone therapy in boys with delayed puberty.
M D C Donaldson and D C L Savage (Bristol).

Delayed puberty, often associated with short stature, is a common problem in the paediatric clinic. These boys' retarded growth and sexual development causes considerable distress during adolescence. Because testosterone is widely believed to accelerate bone maturation disproportionately and thus reduce final height this treatment is often withheld.

Thirty three boys, aged 12·0–17·7 (mean 14·8) years, were treated with testosterone oenanthate (125 mg intramuscularly) monthly for three months They were seen half yearly and heights (Harpenden stadiometer), skeletal maturation (Tanner RUS (TW2), and pubertal status (Tanner and Whitehouse were measured. At six months there was a distinct advance in pubertal status and an increase in height velocity from 4·4 to 9·7 cm/year The boys' morale and confidence increased impressively No serious side effects were seen. The Table shows the effects of treatment on height prediction and height standard deviation score for bone age.

	Baseline	*Five years*	*One year*	*1·5–2 years*
Height SD score for bone age	−·91	−1·17**	−1·09*	−1·[illegible]
Height prediction	166·6	166·3*	167·3*	167·5
No	33	27	11	8

**=p<·05 *=NS compared with baseline

Treatment with testosterone effectively alleviates the main problems of delayed puberty, and our data suggest that at this dosage it has no significant effect on final height.

Antidiuretic hormone release after surgery is appropriate or inappropriate? B A Judd, G B Haycock, and C Chantler (London).

Hyponatraemia following surgery has commonly been attributed to an inappropriate release of antidiuretic hormone (ADH) caused by 'stress'. Whilst ADH levels may be elevated, this may be a physiological response to hypovolaemia. Such a distinction is important as it would lead to different approaches to fluid management We studied two groups of children undergoing routine tonsillectomy, a study group of six children who received intravenous 0·9% saline at 1750 ml/m²/day peri- and postoperatively, and a control group of seven children who received no fluid. We assessed factors associated with hypovolaemia and ADH release. Mean values for each child of levels at 1½, 3 and 6 hours following surgery are shown in the Table.

There was no significant difference in plasma osmolality. The results suggest hypovolaemia occurs in association with raised ADH levels and infusion of saline suppresses this response We would suggest that patients following surgery do not have inappropriately raised ADH levels, and more liberal use of fluids, especially saline should be used.

	Control		*Study*	
	Median	*Range*	*Median*	*Range*
ADH (μU/ml)	12·3	6·16–33	3·85	1·5–7·9*
Noradrenaline (nmol/l)	2·03	1·71–3·0	1·81	1·7–1·91*
Renin ngAI/l/minute	2559	877–8327	1229	571–1755*
Fractional excretion sodium %	27	13–32	68	45–99*
Urine osmolality mosm/kg	914	879–1033	856	309–968*

(*difference from control, p<0·05)

Renal tract abnormalities detected by antenatal ultrasound: the need for a multidisciplinary approach. D Readett, A R Watson, C S Nelson, L Kapila, and M J Mayell (Nottingham).

The more frequent use of antenatal ultrasonography has resulted in the increased detection of fetal renal tract abnormalities. Since many of these would have remained asymptomatic their detection has posed problems with the choice and interpretation of antenatal and postnatal investigations as well as the timing of surgical intervention for lesions whose natural history has not been clearly defined. We report 40 cases investigated in the period 1982–86. Males were more commonly affected than females (2·3:1), and the detection rate increased throughout the study period. Gestational age at detection ranged from 18–39 weeks (mean 32·7 weeks), the majority being detected in the third trimester. Most cases were reported as showing cystic change or hydronephrosis with few specific diagnoses Fetal surgery was undertaken in two cases, which, in retrospect, did not require intervention. Patients were investigated postnatally by a combination of ultrasound radio-isotope scans, MCU, and IVP Diagnoses included PUJ obstruction (45%); multicystic kidney (12%); vesicoureteric reflux (10%), and VUJ obstruction (10%). Four patients died within 14 days of birth (one with chromosomal abnormality). Twenty six of the 40 patients had surgical procedures with pyeloplasty (40%) being the commonest operation. Close cooperation between all those involved in the care of the mother and child is essential if accurate counselling is to be provided, inappropriate surgical intervention avoided, and the natural history defined.

Blood pressure and cerebral injury in sick very low birthweight infants. A Watkins, C West, and R W I Cooke (Liverpool).

Cerebral injury from haemorrhage and ischaemia is a major cause of poor outcome in intensive care of very low birthweight infants. Current hypotheses suggest that impaired cerebral autoregulation allows blood pressure to be the main determinant of cerebral blood flow; hypertension and high flow causing haemorrhage, and hypotension producing low flow and ischaemia.

Hourly systolic, diastolic, and mean blood pressures were recorded directly on 135 very low birthweight infants in intensive care during the first four days of life. Values for survivors and not affected by drug administration were used to derive weight/age centiles. In the whole group ultrasound evidence of intraventricular haemorrhage correlated well with periods of hypotension, but not of hypertension. Ischaemic lesions did not correlate well with periods of hypotension, but were associated with previous haemorrhage. The findings suggest that hypotension predisposes to primary intraventricular haemorrhage and that later parenchymal ischaemic lesions relate to local factors (possibly related to thrombus formation) rather than systemic hypotension.

Mean arterial pressure and neonatal cerebral lesions. V M Miall-Allen, L S de Vries, and A G Whitelaw (London).

In the sick neonate lacking cerebral autoregulation, periventricular haemorrhage (PVH) and periventricular leukomalacia (PLV) have been attributed to excessive and insufficient cerebral blood flow, respectively

In this study we used computed continuous acquisition of direct mean arterial blood pressure (MAP), together with high resolution cranial ultrasound scanning in 33 infants of gestational age 26–30 weeks. Any infant with a significant lesion at the start of recording was excluded. Scans were classified independently into normal, mild, or transient changes, and persistent severe lesions (large PVH ± parenchymal extension or cystic PVL), or death within 48 hours of birth Twelve infants (mean birth weight 1040 g, mean gestational age 27·8 weeks) maintained MAP of $\geqslant 30$ mmHg and had no severe lesions; 21 infants (mean birth weight 1060 g, mean gestational age 27·7 weeks) had MAP below 30 mmHg for > one hour, and nine of these had severe cerebral lesions ($p<0 \cdot 01$) The periods of low MAP preceded the appearance of the lesions.

Intervention to maintain MAP should be further evaluated in terms of its effect on morbidity and mortality of sick neonates, and the underlying mechanisms causing hypotension deserve further investigation.

Intellectual outcome following congenital CMV infections. S Logan (London).

It has been suggested that children with congenital CMV infection, even if apparently asymptomatic, may suffer minor damage leading to intellectual deficit To examine this hypothesis 103 congenitally infected children have been followed up with matched controls for between nine months and six years The cases were identified by screening some 30 000 newborns at three London hospitals for the presence of cytomegalovirus.

To assess their intellectual development Griffiths assessments were performed at 2 years and Weschler preschool and primary scale of intelligence tests at 5 years. Nine children with bilateral moderate to severe sensorineural hearing loss and/or cerebral palsy were identified. When these children were excluded from the analysis, no significant differences were found between cases and controls on either of the outcome measures.

In conclusion, there was no evidence to suggest that apparently undamaged children suffered any ill effects from congenital cytomegalovirus infection. Furthermore, all children with significant handicap were identified by 9 months, so parents with asymptomatic children may be reassured.

Improved primary care does not prevent the admission of children to hospital. T P Hutchison, L Durojaiye, and R J Madeley (Nottingham)

In Nottingham Health District a study has been carried out whose aims were: (i) to compare acute paediatric medical admissions in 1985 with those in 1975 and to relate any differences to changes in services; (ii) to measure the numbers of preventable admissions, working on the hypothesis that this would give an indication of the performance of community services.

A structured questionnaire was completed with parents and information obtained from notes of all children admitted with acute medical problems during October 1985 Results were compared with a similar study undertaken in 1975 by Wynne and Hull on children from the same catchment area. Further information for all health districts in Trent Region was obtained from hospital activity analysis data relating to these 10 years.

There has been a 100% increase in children's admissions in Nottingham, with similar increases throughout Trent Region. Apart from ingestions, there are increases in every diagnostic category, with a six-fold increase in the admission rate for lower respiratory tract problems, mostly asthma and wheeze. There were only 9% 'social admissions'.

The idea of certain admissions being preventable is not a useful concept. Improvements in primary care have not been accompanied by a fall in hospital admissions.

Neonatal rickets: evidence for prenatal abnormality of phosphate balance. P Holland, J Diez, D Linsell, and A R Wilkinson (Oxford).

Thirty babies birth weight <1500 g, had weekly measurements of plasma calcium, phosphate, creatinine, and alkaline phosphatase. A urine sample collected at the same time was analysed for calcium, phosphate, and creatinine, and the tubular reabsorption of phosphate (TRP) and calcium (TRCa) calculated using a standard formula. Radiography of the wrist was performed between four to five weeks. Plasma phosphate and TRCa were the best predictors of those babies who subsequently developed rickets. The reduced TRCa was directly associated with the degree of phosphate depletion and could be corrected by supplementation. Radiographic evidence of rickets was found in 14 babies (50%); seven had severe phosphate depletion at the time of the first sample, suggesting that the phosphate depletion was of prenatal onset. Those babies who subsequently developed rickets could be predicted (80% by week two, 100% by week three). Supplementation with phosphate, sufficient to cause a fall in the TRP, reduced the incidence of rickets. In five babies there was a reduced TRP associated with a low phosphate and calcium which responded to calcium supplementation (secondary hyperparathyroidism). There was no evidence of immaturity of the renal tubule with a tubular reabsorption of >95%. Serial monitoring of TRP and TRCa is a simple and reliable way to predict babies who will develop rickets and is valuable in the monitoring of preventive therapy.

Fine motor performance in 6 year old extremely low birthweight survivors. N Marlow, E L Roberts, and R W I Cooke (Liverpool).

With the exception of gross impairments, detailed motor perfomance of extremely low birthweight survivors is rarely reported. We have studied fine motor performance in 6 year old children with birth weights of <1251 g attending normal school.

Thirty of 33 survivors born in 1980 were examined at school with an age and sex matched classmate as a control. The testing included formal neurological examination, an IQ (WPPSI) and the test of motor impairment (Henderson revision; 1985), which comprises eight tests of manual dexterity, ball skills, and static and dynamic balance.

Two of the study children were in remedial classes, the remainder were in normal classes, including two children with hemiplegia. Study children were significantly more motor impaired (median score 6·0; range: 0–16) compared with controls (2·75; range 0–10) (p=<0·001). On all but six pairings the study child scored higher (worse) than the matched control. These differences persisted after removal of the four children with identified impairments. Although the mean (SE) IQ of the study group (107·5 (2·4)) was lower than those of the control group (117·9 (2·3); p=<0·001). The motor impairment scores were independent of intellectual and other socioenvironmental influences. Extremely low birthweight survivors frequently show significant impairment of motor performance, which if unrecognised, may contribute to school failure.

The association of left ventricular tissue bands with vibratory innocent murmurs. V A Harpin and I Ostman-Smith (Oxford).

Left ventricular tissue bands are found in up to 48% of post mortems and in between 0·4 and 61% of patients referred for echocardiography. They are generally not considered to be clinically important but have been associated in some cases with systolic murmurs. On retrospective analysis of 197 children referred to our cardiac clinic with asymptomatic murmurs, 83% had left ventricular tissue bands. A prospective study was therefore commenced. Fifty five children with asymptomatic systolic heart murmurs were examined, assigned to a diagnosis, and then underwent echocardiography blindly by a second observer. Mean age at examination was 3 years 6 months. Mean age when murmur was first heard was 2 years 8 months (range 0–10 years). Forty nine per cent had a family history of presumed innocent murmurs and 13% of heart disease. All had ECG and CXR within normal limits. Most had grade 2/6 murmurs (64%); 29% were grade 3/6. All except one were vibratory. Fifty three per cent radiated to the neck, 16% had early systolic clicks. On echo, 89% had an apical left ventricular band, which in 49% was associated with another finding; 16% had bands in the left ventricular outflow tract, 45% had asymmetrical aortic valves, and one a bicuspid valve. Fifty two of 55 were exactly defined by the blinded examiner.

Left ventricular tissue bands are the only morphological basis for a vibratory Still's murmur. Recognition of this common diagnosis could prevent many 'routine' cardiac follow ups and unnecessary antibiotic prophylaxis. Asymmetrical tricuspid aortic valves are a significant cause of asymptomatic murmurs in childhood.

Seasonal variation of glycosylated haemoglobin in children with diabetes mellitus. C D Ferrie, T C, Sharpe, D A Price, and R A H Surtees (Manchester).

The clinical impression that glycaemic control in children with diabetes is worse in the winter was tested by determining whether a seasonal variation in glycosylated haemoglobin (HbA_1) exists. One hundred and twenty five patients with a minimum of four estimations of HbA_1 available were studied. HbA_1 levels were measured by an ion exchange column method and seasonal variation was analysed by cosinor-rhythmometry. There was a significant seasonal variation in HbA levels ($p<0·001$) with a peak in mid February and a nadir in mid August. The mean HbA_1 value was 9·93% (SD 0·06%) and the mean amplitude of oscillation was 0·34%, with 95% confidence limits of 0·16% and 0·53%.

It is concluded that there is a seasonal variation of glycaemic control as reflected by HbA_1 levels, but because it is small it is unlikely to be of importance in the clinical management of most diabetic children, however, in a minority, for whom variation of glycaemic control is greater, adjustments in treatment may be indicated.

Sexual abuse, the beginning of an epidemic. C J Hobbs and J M Wynne (Leeds).

In the past two years we have seen 306 children with definite or probable sexual abuse. There were 218 girls (mean age 7·85 years) and 88 boys (mean age 8·12 years), the youngest child was 4 months (Table).

0–5 years		*6–10 years*		*11–15 years*		*Over 15 years*	
Girls	*Boys*	*Girls*	*Boys*	*Girls*	*Boys*	*Girls*	*Boys*
75	27	72	31	57	24	14	6

The abuses included fondling, touching, masturbation, oral, anal, and vaginal intercourse, as well as involvement in pornography and prostitution. Anal abuse was common in both sexes alike at all ages. Natural fathers were the commonest perpetrators but women also abused. Children presented following disclosure or non-accidental injury with physical or psychosomatic symptoms, disturbance in behaviour. or after detection of abuse in another child.

Association with other forms of abuse was common Referrals were received from parents, health and social work professionals, schools, nurseries and police Multidisciplinary assessment included case conferences.

Paediatricians need to be prepared to recognise and manage this emerging problem.

Changes in genetic counselling for cistic fibrosis since discovery of DNA polymorphisms linked to the gene. M Super (Manchester).

At the time of the discovery of DNA probes linked to the cystic fibrosis (CF) gene, more than half the parents of children at the cystic fibrosis clinic at Royal Manchester Children's Hospital had already had sterilisation. Of the 17 couples still fertile and together, all expressed interest in having their genotypes tested, and seven, all parents of younger children, said that they would undertake further pregnancies if testing proved the family informative. None of these would have planned pregnancies before the existence of tests.

Genetic counselling of such parents has suddenly become very factual, with a basic discussion on DNA polymorphisms and the mechanics of prenatal diagnosis using these methods being needed. There are various options which alter, depending on the genotype and the proximity of the exact probes that show linkage to the cystic fibrosis locus. One can offer very accurate prenatal diagnosis or exclusion in the first trimester—often but not always. Some couples are not interested in second trimester tests, which are sometimes needed.

Genotyping of families should be undertaken before the onset of pregnancies to help couples exercise their options coolly. Until simple cures for cystic fibrosis are discovered there will be increased requests for prenatal diagnosis.

Causes and associations of severe specific disorders of speech and language. R J Robinson (London).

I studied 82 children with severe and persistent specific language disorders, looking for possible causal factors.

The study confirms the well known excess of boys (sex ratio 3·8:1), and the familial tendency; 40% of the children had a family history of speech disorder, and 1 in 5·2 of their siblings was also affected.

Twenty seven per cent of the children had a definite pre-, peri-, or postnatal factor which could plausibly account for their specific language disorder.

There was an association with seizures, which had occurred in at least 21% of the children.

A miscellaneous collection of disorders or variants was found more commonly in these children than in the normal population. These included left handedness (29%), clumsiness (abnormal Stott score in 89%), walking after 18 months (22%), undescended testicles (11% of boys), and being a twin (7·5%).

Specific development language disorders cannot be accounted for by a single causal factor. Based on the hypothesis of Geschwind and Galaburda, I suggest that they are the result of interference with development of the left cerebral hemisphere from various factors, with males being more vulnerable, and that these factors may lead to a number of associated anomalies.

Campylobacter pyloridis in children. E J Eastham and T S M Elliott (Newcastle upon Tyne).

The spiral bacterium *Campylobacter pyloridis* has been recently implicated in adults as the aetiological agent in type-B non-immune gastritis and also possibly in duodenal ulceration. The former condition is frequently missed at endoscopy unless biopsies are taken, but this is not done routinely in paediatric practice. We have therefore performed antral biopsies on all children undergoing upper GI endoscopy in our hospital during the past eight months. So far, six (20%) of 30 cases have shown histologically active gastritis with positive cultures for *C pyloridis*. None of these children had duodenal ulcers, and in only three were there visible changes—a fine lymphoid nodular hyperplasia. In addition, in every case (and in none of the remainder) there were circulating specific *C pyloridis* IgG antibodies, all in very high titres. Eradication of the organism with antibiotics and a bismuth preparation has resulted in total resolution of symptoms and histological improvement. We suspect that this organism may be an important causative agent in paediatric upper GI symptomatology, and feel that routine antral biopsies should be performed for both culture and histology in all children being endoscoped for diagnostic purposes.

Renal transplantation in children less than 5 years of age. S P A Rigden, M Bewick, C Chantler, G B Haycock, and G Koffman (London).

Between September 1979 and May 1986, 28 children (23 boys, five girls) aged less than 5 years (mean age 2 years 10 months, range 9 months to 4 years 11 months) have received 33 renal transplants. Four children have been retransplanted, one twice. There were 30 cadaveric grafts and three from live related donors. The mean weight at transplantation was 11·3 kg (range 7·0–19·0 kg). Primary diagnoses were renal dysplasia in 18 patients, congenital nephrotic syndrome in five, nephronophthisis in two, and one case each of polycystic kidney disease, haemolytic uraemic syndrome, and glomerulonephritis. Twenty one grafts were performed using prednisolone and azathioprine immunosuppression, and since October 1983, 12 with cyclosporin A and low dose prednisolone.

The five year actuarial patient survival is 78%; six children have died, five following graft failure, which in three resulted from renal artery stenosis. The five year actuarial survival of the 28 first grafts is 64%; causes of graft loss were acute rejection (one case), chronic rejection (two), arterial thrombosis (one), technical failure (one). Three of the five retransplants were lost within two weeks. Mean GFR (±SD) was 67 (20)ml/min/1·73m^2 SA one year post-transplant (17 patients) and 70 (23)ml/min/1·73m^2 SA five years post-transplant (seven patients). Mean height SDS improved from −2·81 at transplantation (17 children) to −0·95 (7 children) five years later.

These results are comparable with those obtained in older children and support the contention that renal transplantation is the treatment of choice for even very young children with end stage renal disease

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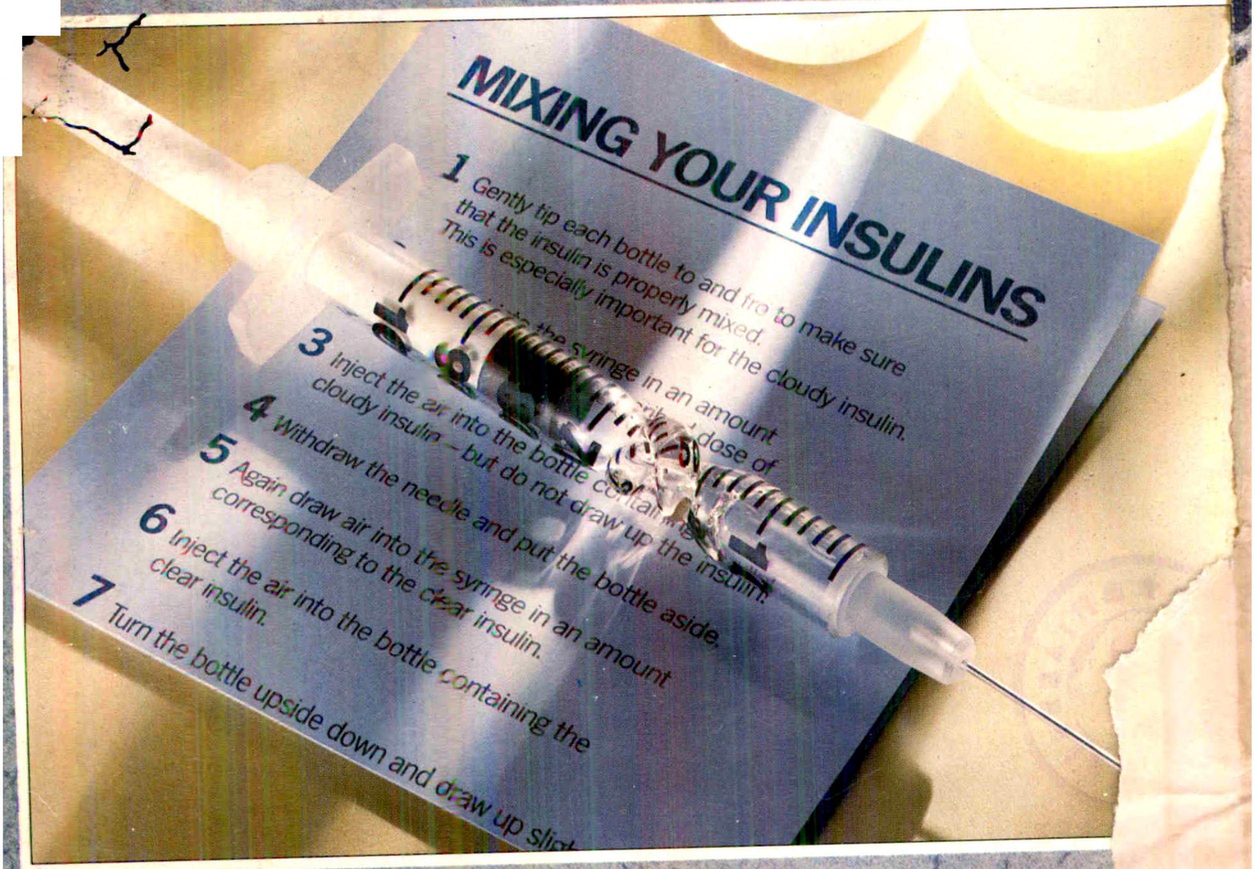
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dose of
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Side and Adverse Effects: Hypoglycaemia. Local reactions, lipodystrophy and hypersensitivity reactions are rarely reported with human insulins.
Pharmaceutical Precautions: Store between 2 – 8°C, protected from sunlight. Insulin which has been frozen should not be used.
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